CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching from an Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Regimen or a Tenofovir Disoproxil Fumarate Containing Regimen to Fixed-Dose Combination of Bictegravir /Emtricitabine/Tenofovir Alafenamide in Elderly, Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 65 Years	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	125,589	
EudraCT Number:	2017-003428-61	
Clinical Trials.gov Identifier:	NCT03405935	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-380-4449	
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching from an Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Regimen or a Tenofovir Disoproxil Fumarate Containing Regimen to Fixed-Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Elderly, Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 65 Years
IND Number:	125,589
EudraCT Number:	2017-003428-61
Clinical Trials.gov Identifier:	NCT03405935
Study Centers Planned:	Approximately 30 centers in Europe
Objectives:	The primary objective of this study is: • To characterize the virologic efficacy of switching virologically suppressed subjects on an E/C/F/TAF FDC or TDF-containing regimen to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 24 The secondary objectives of this study are: • To characterize the safety and tolerability of switching to B/F/TAF FDC from an E/C/F/TAF FDC or TDF-containing regimen through Week 96 • To characterize the virologic efficacy of switching to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 48, Week 72 and Week 96.

Study Design:	Open-label, multicenter, single arm study to evaluate switching from either E/C/F/TAF FDC, or TDF and FTC-containing 'backbone' regimen plus a third agent to bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (B/F/TAF) FDC in virologically-suppressed, HIV-1 infected subjects aged ≥ 65 years. All eligible subjects who complete GS-US-292-1826, Week 48 and are at least 65 years old at the screening visit will be allowed to enter. Subjects can proceed directly into the study after the GS-US-292-1826 study 30-day Follow-Up visit or the subject may enroll even if the subject has already completed and left the prior protocol, as long as the subject remains virologically suppressed on a stable regimen. A stable regimen is defined by no change in the ARV regimen for ≥3 months prior to the screening visit. Subjects not previously participating in GS-US-292-1826 will be able to enroll as long as they meet all eligibility criteria. The GS-US-292-1826 30-day Follow-Up visit may coincide with the Screening visit for this study. Labs drawn during this visit may be utilized for this study as long as the labs are within 30 days of the Day 1 visit. Subjects will be treated for at least 96 weeks.
Number of Subjects Planned:	Approximately 80 subjects in total
Target Population:	All subjects ≥65 years old at the time of the screening visit who are currently receiving either E/C/F/TAF FDC or a TDF-based regimen are eligible to enroll as long as the subject meets all eligibility criteria.
Duration of Treatment:	Treatment duration is at least 96 weeks. At the Week 96 Visit, subjects in a country where B/F/TAF FDC is not yet commercially available, will be given the option to receive B/F/TAF FDC for up to an additional 48 weeks (up to week 144) and attend study visits every 12 weeks followed by 30 Day Follow-Up visit; or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. Subjects who complete the study through Week 96 Visit and do not further continue participation in the study, will be required to return to the clinic 30 days after the Week 96 Visit for a 30-Day Follow-Up Visit.

Diagnosis and Main Eligibility Criteria:	Medically stable HIV-1 infected subjects who meet the following criteria: • Age ≥ 65 years • Currently receiving an ARV regimen of E/C/F/TAF FDC (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for ≥ 3 months • Documented plasma HIV-1 RNA < 50 copies/mL during treatment with E/C/F/TAF (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for the last 2 visits 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) A) Unconfirmed virologic elevations of ≥ 50 copies/mL but < 400 copies/mL (transient detectable viremia, or "blip") in the past are acceptable. B) 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 after < 50 copies/mL has been achieved. • Adequate renal function, an eGFR ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance
Study Procedures/ Frequency:	After Screening procedures, study visits will occur at Day 1, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96. Laboratory analyses (chemistry, hematology, and urinalysis), HIV-1 RNA, CD4+ cell count, assessment of adverse events and concomitant medications, and complete or symptom directed physical examinations will be performed at all study visits. Subjects screening visit should be performed within 30 days from the Day 1 visit to determine eligibility for this study. The GS-US-292-1826, 30 Day Follow-Up visit may be utilized for this study's Screening visit if Day 1 is within 30 days. Any assessments that are over 30 days prior to Day 1will need to be repeated for the current study. Blood and urine for selected evaluations of renal safety, inflammation, and platelet and coagulation function will be collected at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84 and 96. A portion of the biomarker blood sample obtained at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84 and 96 may be utilized to assess study drug PK. This will be a random sample with the date and time of the subject's last medication dose recorded Adverse events and concomitant medications will be assessed at each visit.

Test Product, Dose, and Mode of Administration:	bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (B/F/TAF) FDC administered orally, once daily, without regard to food
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	• Adverse events through Week 24 • Adverse events through Week 48 • Adverse events through Week 72 • Adverse events through Week 96
Efficacy:	Primary Endpoint: • HIV-1 RNA <50 copies/mL at Week 24 - defined by the Food and Drug Administration (FDA) snapshot algorithm. Secondary Endpoints: • HIV-1 RNA <50 copies/mL at Week 48 - defined by the Food and Drug Administration (FDA) snapshot algorithm. • HIV-1 RNA <50 copies/mL at Week 72 - defined by the Food and Drug Administration (FDA) snapshot algorithm. • HIV-1 RNA <50 copies/mL at Week 96 - defined by the Food and Drug Administration (FDA) snapshot algorithm.
Patient reported outcomes:	Health related questionnaires will be administered, including the Visual Analogue Scale (VAS), HIV Treatment Satisfaction (HIVTSQ), EQ-5D, Short Form 36 Health Survey (SF-36), and Functional Assessment of Chronic Illness Therapy − Fatigue (FACIT-F).

Statistical Methods:	The sample size is based on feasibility of conducting a study with ≥65 years old subjects. The efficacy endpoints will be characterized by a point estimate and 95% confidence intervals. Descriptive statistics will summarize baseline characteristics, efficacy, safety, and patient reported outcomes data.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ABC/3TC	abacavir/lamivudine, Epzicom®, Kivexa®
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	Antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BUN	blood urea nitrogen
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide, GS-9883/F/TAF, Biktarvy
CBC	complete blood count
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CNS	central nervous system
COBI, /co	cobicistat, C, (GS-9350)
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DRV	Darunavir
PV&E	Pharmacovigilance and Epidemiology
DTG	dolutegravir, Tivicay®
ECG	Electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	Estimated glomerular filtration rate according to the Cockcroft-Gault formula
EVG	elvitegravir, E
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, Genvoya®
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, Stribild®
EQ-5D	EuroQol 5D patient questionnaire
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination

FTC/TAF	emtricitabine/tenofovir alafenamide, F/TAF, Descovy®
FTC, F	emtricitabine, Emtriva®
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GLSM	geometric least squares mean
GSI	Gilead Sciences, Inc.
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HIV TSQ	HIV Treatment Satisfaction Status Questionnaire
IB	investigator's brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
INSTI	integrase strand-transfer inhibitors
IRB	institutional review board
IWRS	interactive web response system
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Mantel-Haenszel
min	Minute
mmHg	millimeters mercury
nM	nanoMolar
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
P-gp	P-glycoprotein
PI	protease inhibitor
PK	Pharmacokinetic
PT	preferred term
PT	prothrombin time
QD	once daily
RAL	raltegravir
RNA	ribonucleic acid
SA	single agent

SAE	serious adverse event
SF-36	Short Form 36 Health Survey
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate, Viread®
TFV-DP	tenofovir diphosphate (TFVpp)
t_{max}	the time (observed time point) of C_{max}
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
VAS	Visual analog scale

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 37 million people worldwide {UNAIDS 2016}. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {Palella 1998}, {Mocroft 1998}, {Sterne 2005}.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand transfer inhibitor (INSTI), the nonnucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, or the boosted protease inhibitor (PI), darunavir (DRV) {European AIDS Clinical Society (EACS) 2017}.Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Sterrantino 2012}, {Aldir 2014}

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

Bictegravir is a potent inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infection {Gallant 2016}. Antiviral testing has shown that bictegravir is active against a broad panel of HIV-1 viral lab strains and clinical isolates. Bictegravir (BIC; B) is a potent INSTI that is being evaluated for the treatment of HIV-1 infection {Gallant 2016} and that has demonstrated a terminal half-life suitable for once daily administration without a boosting agent.

In a Phase 2 study of ART-naive HIV-infected subjects, BIC was compared with the guideline-recommended INSTI, dolutegravir (DTG) {Sax 2017}. When coadministered with the guideline-recommended N(t)RTI backbone, emtricitabine (FTC; F) and tenofovir alafenamide (TAF), each INSTI demonstrated high ARV activity, with no virologic failures due to resistance, and both treatments were safe and well tolerated.

Gilead Sciences (Gilead) has coformulated bictegravir with the NRTI emtricitabine (FTC; F) and the NtRTI tenofovir alafenamide (TAF) into an FDC tablet that is suitable for once-daily use. This bictegravir/F/TAF FDC may provide a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection. Phase 3 studies of the FDC are currently underway and Week 48 results are described in section 1.2.3.4.

1.2. Bictegravir

1.2.1. General Information

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

1.2.2. Preclinical Pharmacology and Toxicology

A core battery of safety pharmacology studies have been conducted with bictegravir. 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 bictegravir on all major organ systems. The volume of distribution of bictegravir ranged between 0.09 and 0.22 L/kg in the preclinical species, which indicates that the distribution of bictegravir is limited to the extracellular compartment due to its high binding to plasma proteins. The projected half-life of bictegravir in humans is approximately 20 hours based upon the estimates of clearance and volume of distribution.

1.2.2.1. Pharmacology

Bictegravir has IC_{50} values ranging from 1.5 to 2.4 nM, similar to the inhibitory effect of DTG and EVG. Bictegravir 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. Bictegravir does not show significant cytotoxicity against dividing and non-dividing human PBMCs, primary human hepatocytes and various non-target human cell lines. Bictegravir is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase UGT1A1 and secondarily by CYP3A. Bictegravir does not inhibit major human CYP isoforms or UGT1A1 at concentrations up to 25 μM. Consequently, Bictegravir 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. Bictegravir only modestly inhibits renal transporter OCT2

(IC_{50} = 0.42 μM). As a result, bictegravir 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 bictegravir will affect the OCT2-mediated excretion of co-administered drugs is considered to be low.

Bictegravir 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, bictegravir 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 bictegravir 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 bictegravir 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, bictegravir was well-tolerated with no bictegravir-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, bictegravir exposures in the rat were considered to be approximately 12-/31-fold higher (males/females) than the projected steady state human exposure of bictegravir following administration of bictegravir/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 bictegravir 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, bictegravir-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 bictegravir-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 bictegravir/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 bictegravir. 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 Bictegravir

Clinical trials entailing the use of bictegravir 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 bictegravir 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 bictegravir 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 Bictegravir 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 Bictegravir/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a Bictegravir (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 Bictegravir, Emtricitabine and Tenofovir Alafenamide When Administered as Bictegravir/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 Bictegravir 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 Bictegravir 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 Bictegravir 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 Bictegravir in healthy subjects (completed)

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

- GS-US-141-1487, a Phase 1 randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of Bictegravir on Renal Function as Assessed by Markers of Glomerular Filtration Rate (completed)

- GS-US-311-1790, a Phase 1Randomized, Open Label, Drug Interaction Study Evaluating the Effect of F/TAF FDC Tablet or Bictegravir 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 Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (Bictegravir/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets (completed)

- GS-US-380-1991, a Phase I Single and Multiple Dose Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (Bictegravir/FTC/TAF) in Healthy Japanese and Caucasian Subjects (ongoing)

- GS-US-380-1999, a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Bictegravir/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 Bictegravir/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 Bictegravir Pharmacokinetics (completed)

- GS-US-141-1475, a Phase 2 Randomized, Double-Blinded Study of the Safety and Efficacy of Bictegravir + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults (ongoing)

- GS-US-380-1489, a Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults (ongoing)

- GS-US-380-1490, a Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults (ongoing)

- GS-US-380-1844, A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed (ongoing)

- GS-US-380-1878, 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 (ongoing)

- GS-US-380-1961, A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women (ongoing)

- GS-US-380-1474, A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Virologically Suppressed Adolescents and Children (ongoing)

- GS-US-380-4030, A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and Either Emtricitabine/Tenofovir Alafenamide or Emtricitabine/Tenofovir Disoproxil Fumarate to a Fixed Dose Combination of Bictegravir/ Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected Subjects who are Virologically Suppressed (ongoing)

Please refer to the B/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 bictegravir 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 bictegravir. 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 bictegravir in healthy subjects.

There was no difference in the overall incidence or type of AEs when bictegravir was administered in the fasted and fed states. There was no difference in the overall incidence of AEs when bictegravir 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 bictegravir monotherapy for 7 days and 100 mg bictegravir with FTC/TAF for 7 days, the mean serum creatinine change at Day 7 was 0.14 mg/dL following bictegravir and 0.17 mg/dL following bictegravir + FTC/TAF. All changes returned to baseline after discontinuation of bictegravir.

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 bictegravir was characterized by rapid absorption with time to peak plasma concentrations (median T_{max} of cohorts) ranging between 1 and 4 hours following administration under fasted conditions.

bictegravir exposures were appropriately dose proportional following single dose 25-100 mg dose administration, with decreasing dose proportional at higher doses. The half-life of bictegravir was approximately 18 hours, with no changes observed across studied dose range as evidenced by parallel terminal phase slopes. A high-fat meal increased AUC_{inf} and C_{max} (geometric mean, 84% and 101%, respectively) following 100 mg single dose administration. Steady state was achieved after 4-6 days of once daily dosing of bictegravir with average accumulation ratios for AUC_{24hr} of 1.6.

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

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

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

Table 1-2 presents bictegravir plasma PK parameters following administration of bictegravir (5, 25, 50, 100, and 300 mg) once daily for 7 days. Following administration of either bictegravir (5, 25, 50, 100, or 300 mg) once daily for 7 days, the PK absorption profile observed on Days 1 and 7 was similar to that observed in Part A (SAD). The median T_{max} values ranged from 1.5 to 2.5 hours on Day 1 and 1.5 to 4.0 hours on Day 7. Linearity was observed comparing bictegravir AUC and C_{max} on Days 1 and 7 over the dose range of 25 to 50 mg. Steady state levels of bictegravir 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 bictegravir (approximately 18 hours).

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

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

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

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

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

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

CI = confidence interval; GLSM = geometric least squares mean

1.2.3.2. Phase 1b Proof of Concept

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

Bictegravir 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 bictegravir.

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 bictegravir. 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.

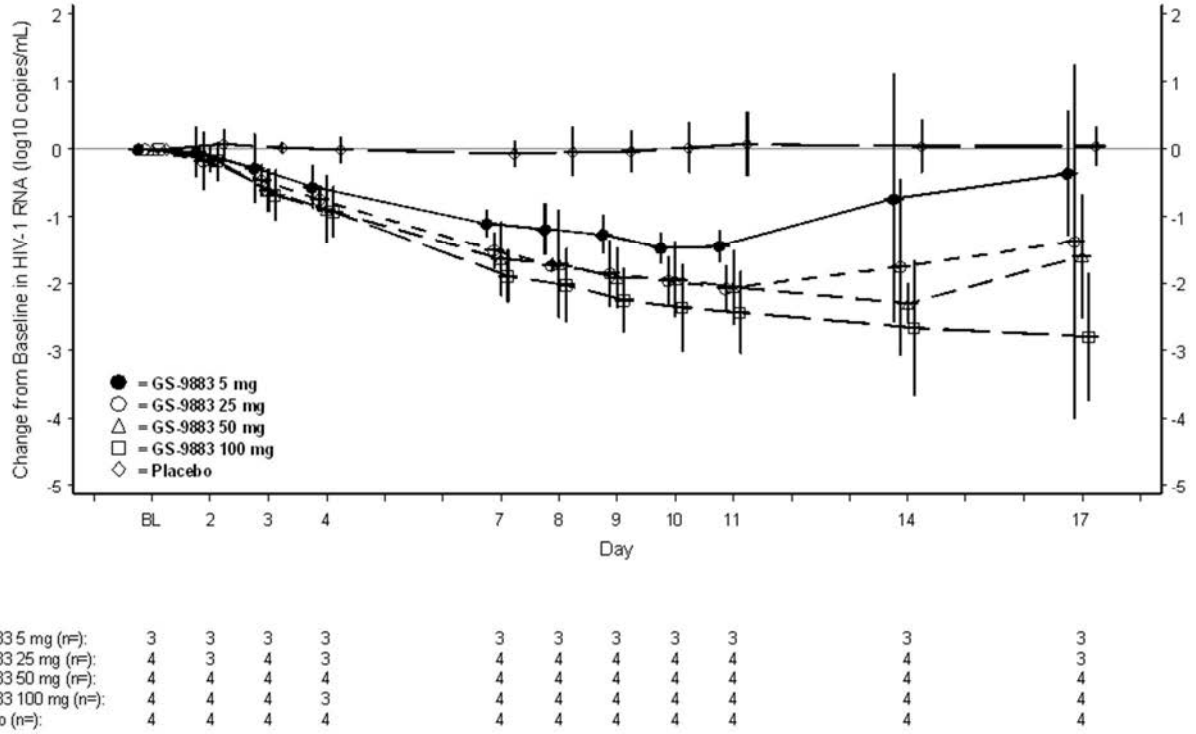
Table 1-4. Trough Bictegravir Plasma Concentrations at Steady State Following Bictegravir Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ_{95} Values (Bictegravir PK Analysis Set)

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

a The protein adjusted IQ_{95} ($paIQ_{95}$) value is estimated based on steady-state C_{tau} values and the in vitro $paIC_{95}$ value for wild-type HIV-1 (162 ng/ml).

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

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



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

Mean viral load change on Day 11 was -2.08 log_{10} in the 25 mg cohort, -2.06 log_{10} in the 50 mg cohort, and -2.43 log_{10} in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was -0.92 log_{10} in the 5 mg cohort, -1.33 log_{10} in the 25 mg cohort, -1.37 log_{10} in the 50 mg cohort and -1.61 log_{10} in the 100 mg cohort. Viral suppression (HIV-1 RNA < 50 copies/mL) was ever achieved by the end of the study (Day 17) by 1 subject (25.0%) in the bictegravir 50 mg group and 2 subjects (50%) in the bictegravir 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 bictegravir+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: Bictegravir 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 bictegravir 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 bictegravir+F/TAF group and 33 subjects in the DTG+F/TAF group. At the time of the Week 24 data analysis, 2 subjects (2.0%) had prematurely discontinued from the study, 1 in each treatment group; both subjects were lost to follow-up.

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

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

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

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

Efficacy Results

Virologic success at Weeks 12 and 24 was assessed using the US FDA-defined snapshot algorithm, defined as plasma HIV-1 RNA < 50 copies/mL. At Weeks 12 and 24, virologic success was high and similar between the 2 treatment groups as follows: Week 12 bictegravir+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 bictegravir+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: Bictegravir+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: Bictegravir+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: Bictegravir+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: Bictegravir+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:

- **Bictegravir+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 bictegravir+F/TAF group; this event was also reported as an SAE. One other SAE (appendicitis), also in the bictegravir+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: Bictegravir+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 bictegravir+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: Bictegravir+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: Bictegravir+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 (bictegravir+F/TAF, 7.8% [5 subjects]), fasting serum glucose (DTG+F/TAF, 6.3% [2 subjects]), aspartate aminotransferase (AST) (bictegravir+F/TAF, 3.1% [2 subjects]), and fasting low-density lipoprotein (LDL) (bictegravir+F/TAF, 3.1% [2 subjects]). The only Grade 4 laboratory abnormalities were for creatine kinase, reported in 2 subjects (3.1%) in the bictegravir+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: Bictegravir+F/TAF 0.12 (0.06, 0.18) mg/dL; DTG+F/TAF 0.13 (0.05, 0.21) mg/dL. There were decreases in median (Q1, Q3) $eGFR_{CG}$ at Week 24, which were smaller in the bictegravir+F/TAF compared with the DTG+F/TAF group: Bictegravir+F/TAF −13.3 (−19.9, −4.0) mL/min; DTG+F/TAF −17.2 (−25.7, −6.9) mL/min.

Conclusions

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

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

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

- No AEs led to study drug discontinuation in either treatment group.

- Both bictegravir+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 bictegravir+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.

1.2.3.4. Summary of B/F/TAF Phase 3 Studies

Summary of Phase 3 Study (GS-US-380-1489)

Results from a blinded phase 3 study were reported that compared B/F/TAF FDC to coformulated abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC) {Gallant 2017}. HIV-infected, treatment-naïve, HLA-B*5701-negative, HBV-uninfected adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min were randomized 1:1 to receive blinded treatment with fixed-dose combination B/F/TAF (50/200/25 mg) or ABC/DTG/3TC (600/50/300 mg) with matching placebos once daily. The primary endpoint was proportion of participants with HIV-1 RNA (VL) < 50 c/mL at W48 (FDA snapshot). Noninferiority was assessed through 95.002% confidence intervals (CI) (12% margin). Secondary endpoints were safety (adverse events [AEs] and laboratory abnormalities) and pre-defined analyses of changes from baseline in bone mineral density (BMD) and measures of renal function, including eGFR and proteinuria. Six hundred and twenty nine participants were randomized and treated (314 B/F/TAF, 315 ABC/DTG/3TC): 10% women, 36% Black, 16% VL >100,000 c/mL, 11% CD4 < 200 cells/mL. Median baseline characteristics: age 32 yrs, CD4 count 444 cells/μL, and VL 4.47 log10 c/mL. At W48, B/F/TAF was noninferior to ABC/DTG/3TC, with 92.4% on B/F/TAF and 93.0% on ABC/DTG/3TC

achieving HIV-1 RNA < 50 c/mL (difference -0.6%; 95.002%CI -4.8% to 3.6%, p=0.78). No resistance mutations emerged in either group. Comparing B/F/TAF to ABC/DTG/3TC throughout, the most common AEs were diarrhea (13%, 13%), headache (11%, 14%), and nausea (10%, 23%). Few participants (0 vs 4 [1%]) had any AEs leading to premature study drug discontinuation. At W48, mean % changes from baseline in BMD were -0.83% vs. -0.60% (p=0.39) [lumbar spine] and -0.78% vs. -1.02% (p=0.23) [total hip]. No differences between treatments were noted in changes from baseline for eGFR and proteinuria at W48. At W48, B/F/TAF achieved virologic suppression in 92.4% of treatment-naïve adults and was noninferior to ABC/DTG/3TC, with no emergent resistance. B/F/TAF was safe and well tolerated with less nausea than ABC/DTG/3TC. Bone and renal safety profiles were similar between groups.

Summary of Phase 3 Study (GS-US-380-1490)

A second phase 3 study compared BIC and DTG, each with F/TAF, utilizing a single-pill coformulation of B/F/TAF {Sax 2017}. Treatment-naïve, HIV-infected adults with estimated glomerular filtration rate (eGFR) ≥30 mL/min were randomized 1:1 to receive blinded treatment with fixed dose combination B/F/TAF (50/200/25 mg) or DTG (50 mg) + F/TAF (200/25 mg) with matching placebos once daily through W48. Chronic hepatitis B and/or C infection was allowed. The primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL (c/mL) at W48 (FDA snapshot). Noninferiority was assessed through 95.002% confidence intervals (CI) using a margin of 12%. Secondary endpoints were safety measures (adverse events [AEs] and laboratory results). There were 645 participants randomized and treated (320 B/F/TAF, 325 DTG + F/TAF): 12% women, 31% Black, 19% viral load (VL) >100,000 c/mL, 12% CD4 < 200 cells/µL, median age 34 yrs, CD4 count 440 cells/µL, and VL 4.44 log10 c/mL. At W48, B/F/TAF was noninferior to DTG + F/TAF, with 89.4% on B/F/TAF and 92.9% on DTG + F/TAF achieving HIV-1 RNA < 50 c/mL (difference -3.5%; 95.002%CI -7.9% to 1.0%, p=0.12). Six subjects discontinued treatment and had no post baseline HIV-1 RNA data for the following reasons: patient decision-3, protocol violation due to incarceration-1, lost to follow-up-1 and investigator discretion-1. Both the Missing=Excluded (M=E) and Missing=Failure (M=F) sensitivity analyses were pre-specified M=E analysis (B/F/TAF vs DTG + FTC/TAF, % treatment difference (95% CI); p-value): 99.0% (288/291) vs. 99.3% (304/306), -0.4% (-2.3, 1.6); p=0.63 Missing values represent a potential source of bias in a clinical trial. Therefore, the study protocol pre-specified the M=E analysis as one imputation method for missing data The M=E population analysis excludes subjects in the full analysis set who do not have HIV-1 RNA data at the efficacy analysis time point. Of note, the M=E analysis set includes subjects with HIV-1 RNA data at the efficacy analysis time point, even if the subject has discontinued study antiretroviral medications but remained “in the study” on non-study antiretroviral medications (for the treatment of HIV). M=F analysis (B/F/TAF vs DTG + FTC/TAF, % treatment difference (95% CI); p-value): 90.0% (288/320) vs. 93.5% (304/325), -3.4% (-7.7, 0.9); p=0.12. The study protocol pre-specified the M=F analysis as a 2nd imputation method for missing data. The M=F population considers subjects in the full analysis set who do not have HIV-1 RNA data at the efficacy analysis time point as having HIV-1 RNA ≥ 50 copies/mL. Of note, the M=F analysis set includes subjects with HIV-1 RNA data at the efficacy analysis time point, even if the subjects has discontinued study antiretroviral medications but remained “in the study” on non-study antiretroviral medications (for the treatment of HIV). At

W48, proportion of participants with HIV-1 RNA ≥50 c/mL was < 1% in each arm. No study subject in either treatment arm developed resistance to any of the study drugs. The most common AEs were headache (13% B/F/TAF, 12% DTG + F/TAF) and diarrhea (12% for both). Few participants (5 [2%], 1 [< 1%]) had AEs leading to premature study discontinuation. Lipid changes were not significantly different between study arms. No renal discontinuations and no cases of proximal renal tubulopathy were reported. After 48 weeks, B/F/TAF achieved virologic suppression in 89.4% of treatment- naïve adults and was noninferior to DTG + F/TAF. B/F/TAF was safe and well tolerated.

Summary of Phase 3 Studies (GS-US-380-1844 and 1878)

One of the ongoing studies is designed to explore the efficacy and safety of B/F/TAF compared to regimens containing dolutegravir (50mg) (DTG) among virologically suppressed patients switching from an existing antiretroviral regimen (Study 1844). The other ongoing study in virologically suppressed patients compares switching to B/F/TAF versus remaining on a suppressive regimen of two nucleoside/nucleotide reverse transcriptase inhibitors and a boosted protease inhibitor (Study 1878). In study 1844, patients (n=520) who were virologically suppressed (HIV-1 RNA levels <50 copies/mL) on a regimen of ABC/DTG/3TC or DTG+ABC/3TC were randomized 1:1 to stay on their existing regimen or switch to B/F/TAF in a blinded manner. Study 1878 is an open-label study in which patients (n=520) who were virologically suppressed on a boosted protease inhibitor of darunavir (800mg) or atazanavir (300mg) plus a nucleoside/nucleotide backbone of ABC/3TC or emtricitabine/tenofovir disoproxil fumarate (200/300mg) were randomized 1:1 to either maintain their current regimen or switch to B/F/TAF. The primary endpoint in these studies is the proportion of patients with HIV-1 RNA ≥50 copies/mL at Week 48, and the lower bound of the 95 percent CI for noninferiority is 4 percent. Both studies were randomized through 48 weeks, after which point patients continuing in the studies enter an open-label extension receiving B/F/TAF. B/F/TAF met the definition of non-inferiority in all four studies, with comparable proportions of patients having HIV1 RNA ≥50 copies/mL (Studies 1844 and 1878). In all studies B/F/TAF was well tolerated and no patients discontinued study medication due to renal events. No patients randomized to the bictegravir or dolutegravir arms developed treatment-emergent resistance. One patient randomized to the protease inhibitor arm in Study 1878 developed an abacavir resistance mutation (L74V).{Gilead Sciences Inc 2017}

1.3. Information about Emtricitabine (Emtriva®, F)

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 an 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 B/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).

- GS-US-311-1717, a Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens containing ABC/3TC (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-292-0104 and GS-US-292-0111, Phase 3 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (ongoing)

- GS-US-292-0109, a Phase 3 open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects (ongoing)

- GS-US-292-0112, a Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide single-tablet Regimen in HIV-1 positive patients with mild to moderate renal impairment (ongoing)

- GS-US-292-0117, a Phase 3, two-part study to evaluate the efficacy of Tenofovir Alafenamide versus placebo added to a failing regimen followed by treatment with Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 positive, antiretroviral treatment-experienced adults (ongoing)

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

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

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

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

Study GS-US-292-0102 is an ongoing, randomized, active-controlled Phase 2 study, compares E/C/F/TAF (10 mg) versus Stribild® (STB, E/C/F/TDF) in treatment-naïve, HIV-1 infected subjects. At Week 48, the E/C/F/TAF demonstrated potent antiviral efficacy (HIV-1 RNA < 50 copies/mL) similar to STB (88.4% [99/112] vs 87.9% [51/58] using the 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 Bictegravir/emtricitabine/tenofovir alafenamide (Bictegravir/F/TAF)

Please refer to the Bictegravir/F/TAF Investigator's Brochure for further information.

1.5.1. GS-US-141-1233: Study of the Relative Bioavailability of Bictegravir, FTC, and TAF between Bictegravir/F/TAF and Bictegravir + 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 B/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets compared with the bictegravir (75 mg) tablet and the F/TAF (200/25 mg) FDC tablet administered simultaneously and 2) the effect of food on the PK of bictegravir, FTC, and TAF when administered as B/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets.

Cohort 1 evaluated the relative BA and food effect of bictegravir/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 B/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, bictegravir AUC_{inf} and C_{max} were 27% and 31% higher, respectively, following B/F/TAF (75/200/25 mg) FDC administration than following administration of single-agent bictegravir (75 mg) with the F/TAF (200/25 mg) FDC. FTC and TAF exposure was similar following administration of B/F/TAF FDC (75/200/25 mg) or single-agent bictegravir (75 mg) with the F/TAF (200/25 mg) FDC.

Compared with administration under fasted conditions, administration of the B/F/TAF (75/200/25 mg) FDC with a high-fat meal resulted in a 46% higher bictegravir AUC_{inf} and a 27% higher bictegravir 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). B/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 B/F/TAF (50/200/25 mg) FDC tablet compared with the single-agent bictegravir (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 bictegravir AUC_{inf} and C_{max} following administration of the 50mg bictegravir FDC tablets was 79% and 78%, respectively of those observed in the same study following co-administration of bictegravir 75 mg single agent with F/TAF (200/25 mg) under fasted conditions. The bictegravir 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 bictegravir with AUC_{inf} increasing by 24%. The steady state $_{pa}IQ_{95}$ of bictegravir/F/TAF (50/200/25 mg) was predicted to be 17 (fasted)-23 (fed). The exposures of TAF and FTC of the 50 mg bictegravir FDC were similar to those of bictegravir 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

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

B/F/TAF FDC has the potential to offer a simple, once-daily regimen containing a INSTI that provides a high barrier to resistance, does not require a boosting agent, and offers an effective and safer alternative to standard nucleos(t)ide based regimens, without the need for HLA testing or close monitoring of renal or bone toxicities. It could provide a FDC treatment that avoids the risk of hypersensitivity reactions, would not contribute to an increased risk of cardiovascular events, could be used in patients with chronic hepatitis B or C infection or renal impairment, and that could be continued as patients age and confront non-HIV-related comorbidities. In the current Phase 3 studies of B/F/TAF, sparse data are available on the efficacy and safety in HIV-infected subjects who are 65 years and older. As the population of people living with HIV infection continues to age (median age approaches 50 years in many locations), the urgency of obtaining B/F/TAF safety and efficacy data in older populations is critical. The study provides the opportunity to evaluate the potential benefits of switching from E/C/F/TAF to B/F/TAF FDC in men and women, as an ongoing study of this switch is underway solely in women.

The objective of this study is to characterize the virologic efficacy of switching virologically suppressed subjects on an E/C/F/TAF FDC or TDF-containing regimen (if currently or previously participated in GS-US-292-1826) to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 24.

1.7. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective anti-retroviral therapy. With the aging of the HIV-infected population such that half of the population is now over the age of 50 years, there is a need for efficacy and safety data in this population. This study seeks to address this gap by enrolling subjects 65 years or older in order to generate data on the efficacy and safety of B/F/TAF FDC in this population. 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. Potential benefits may include provision of a new ARV 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 BIC (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 BIC exposures that were approximately 5-fold above human exposures when given the B/F/TAF FDC. No adverse drug reactions associated with liver or bile duct problems has been identified in humans treated with BIC. 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 7.4). As Phase 3 data have clearly shown the benefits of B/F/TAF FDC outweigh the risks in treatment naïve subjects as well as in ongoing studies in virologically suppressed subjects that switch to B/F/TAF FDC and the potential risk of the study will be mitigated by follow up and monitoring of overall health, the overall benefit-risk assessment for B/F/TAF FDC is favorable. {Gilead Sciences Inc 2017}

1.8. 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 characterize the virologic efficacy of switching virologically suppressed subjects on an E/C/F/TAF FDC or TDF-containing regimen to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 24.

The secondary objectives of this study are as follows:

- To characterize the safety and tolerability of switching to B/F/TAF FDC from an E/C/F/TAF FDC or TDF-containing regimen through Week 96.

- To characterize the virologic efficacy of switching to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 48, Week 72 and Week 96.

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- HIV-1 RNA <50 copies/mL at Week 24 - defined by the Food and Drug Administration (FDA) snapshot algorithm

The secondary endpoints of this study are:

- Adverse events through Week 24
- Adverse events through Week 48
- Adverse events through Week 72
- Adverse events through Week 96
- HIV-1 RNA <50 copies/mL at Week 48 - defined by the Food and Drug Administration (FDA) snapshot algorithm
- HIV-1 RNA <50 copies/mL at Week 72 - defined by the Food and Drug Administration (FDA) snapshot algorithm
- HIV-1 RNA <50 copies/mL at Week 96 - defined by the Food and Drug Administration (FDA) snapshot algorithm

3.2. Study Design

Open-label, multicenter, single arm study to evaluate switching from either E/C/F/TAF FDC or TDF-containing regimen (if currently or previously participated in GS-US-292-1826) to bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (B/F/TAF) FDC in virologically-suppressed, HIV-1 infected subjects aged ≥ 65 years.

All eligible subjects who complete GS-US-292-1826, Week 48 and are at least 65 years old at the screening visit will be allowed to enter. Subjects can proceed directly into the study after the GS-US-292-1826 study 30 day Follow-Up visit; additionally if the subject has already completed and left the study, subject may enroll as long as the subject remains virologically suppressed on a stable regimen. A stable regimen is defined by no change in the ARV regimen for ≥3 months prior to the screening visit.

Subjects not previously enrolled into GS-US-292-1826 will be eligible to enroll as long as they meet all eligibility criteria.

The GS-US-292-1826 30-day Follow-Up visit may coincide with the screening visit for this study. Labs drawn during this visit may be utilized for this study as long as the labs are within 30 days of the Day 1 visit.

Subjects will be treated for at least 96 weeks.

3.3. Study Treatments

Subjects who provide written informed consent and meet all eligibility criteria will receive bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (B/F/TAF) FDC administered orally, once daily, without regard to food.

3.4. Duration of Treatment

The treatment duration is at least 96 Weeks.

At the Week 96 Visit, subjects in a country where B/F/TAF FDC is not yet commercially available will be given the option to receive B/F/TAF FDC for up to additional 48 weeks (up to Week 144) and attend study visits every 12 weeks, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

3.5. End of Study

End of study, for purposes of the primary and secondary analyses, is defined as completion of the 96 weeks of treatment and the 30 Day Follow-Up visit. Subjects who are still on B/F/TAF FDC at Week 96 and continue to attend visits after Week 96, will have the Week 96 study visit, and then attend study visits every 12 weeks for up to additional 48 weeks (up to Week 144) followed by a 30 day Follow-Up visit, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

3.6. Post Study Care

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

3.7. Biomarker Testing

3.7.1. Biomarker Samples to Address the Study Objectives:

Blood and urine will be collected for selected evaluations of bone and renal safety, inflammation, and platelet and coagulation function at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84 and 96. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined is based upon the current state of scientific knowledge. Specific testing may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

Biomarkers to be analyzed will include but will not be limited to soluble: glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer. Inflammation evaluations may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2. Specimens will be collected from all subjects.

Samples may be stored for a period of 15 years.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 80 subjects who meet the eligibility criteria will be enrolled in the study.

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 ≥ 65 years

3) Currently receiving an ARV regimen of E/C/F/TAF FDC (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for ≥ 3 months

4) Documented plasma HIV-1 RNA < 50 copies/mL during treatment with E/C/F/TAF (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for the last 2 visits 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)

    a) Unconfirmed virologic elevations of ≥ 50 copies/mL but < 400 copies/mL (transient detectable viremia, or "blip") in the past are acceptable.

    b) 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 after < 50 copies/mL has been achieved.

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

6) Have no documented or suspected resistance to FTC, TFV, or BIC including, but not limited, to the reverse transcriptase resistance mutations K65R and M184V/I

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

8) Adequate renal function:

   eGFR ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 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: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})} = \text{CLcr (mL/min)}$

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

9) Male subjects who are fertile and engage in heterosexual intercourse with women who are of child-bearing potential must agree to use protocol specified method(s) of contraception as described in Appendix 5.

10) Male subjects must agree to refrain from sperm donation from first study drug dose until after the end of relevant systemic exposure

11) Life expectancy >1 year

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

13) Total bilirubin ≤ 1.5X ULN or normal direct bilirubin

14) 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))

4.3. Exclusion Criteria

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

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

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

3) Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents or systemic steroids (e.g. prednisone doses > 10 mg daily or equivalent) 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) Malignancy within 5 years of screening other than cutaneous Kaposi's sarcoma, completely resected non-melanoma skin cancer (basal cell carcinoma or non-invasive cutaneous squamous carcinoma), or completely resected carcinoma in-situ of the cervix (CIN 3) or anus (AIN 3). A prior malignancy treated with curative therapy and for which there has been no evidence of disease for at least five years prior to screening is allowed.

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 Medical Monitor

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) Known hypersensitivity to B/F/TAF FDC tablets, their metabolites, or formulation excipient

10) Subjects receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with BIC, FTC, TAF:

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

* Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.
** Dofetilde was withdrawn from the EU in 2009.

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

12) Active tuberculosis infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Subject Enrollment

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

Once eligibility has been confirmed and prior to or during the Day 1 visit the Investigator or designee will enroll 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 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.

Subject enrolled will be assigned study drug bottle numbers of B/F/TAF FDC at study visits by IWRS.

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

5.2. Description and Handling

5.2.1. Formulation

B/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with “GSI” on one side of the tablet and “9883” on the other side of the tablet. B/F/TAF tablets contain 50 mg of bictegravir (B, BIC), 200 mg of emtricitabine (F, FTC), and 25 mg of tenofovir alafenamide (TAF). In addition, of the active ingredients, active B/F/TAF tablets contain croscarmellose sodium, microcrystalline cellulose, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, iron oxide red, and iron oxide black.

5.2.2. Packaging and Labeling

B/F/TAF (50/200/25 mg) 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 to be distributed to centers in the 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 (B/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. Keep the bottle tightly closed to protect from moisture. 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 when handling.

5.3. Dosage and Administration of B/F/TAF

B/F/TAF tablets will be provided by Gilead Sciences.

Bictegravir/emtricitabine/tenofovir alafenamide (B/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.

Table 5-1. Prior and Concomitant Medications

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

* Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.
** Dofetilde was withdrawn from the EU in 2009.

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

5.5. Accountability for Investigational Medicinal Product (IMP)

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

B/F/TAF 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 B/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

Entry into Screening does not guarantee enrollment into the study. Please refer to section 5.1 for details about treatment assignment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 30 days before the Day 1 visit to determine eligibility for participation in the study. The GS-US-292-1826 30 Day Follow-Up visit may be utilized for this study's Screening visit if Day 1 is within 30 days. Any assessments that are over 30 days prior to Day 1 will need to be repeated for the current study.

The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history, including: HIV-1 disease-related events, cigarette smoking (including current or previous smoker), history of fractures, family history of myocardial infarction or stroke, and prior medications within 30 days of screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator); if available, obtain historical genotype(s) (not required for entry to study)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Height
- 12-lead ECG performed supine

- Obtain blood and urine samples as described in Sections 6.9 and 6.10

  — $eGFR_{CG}$

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

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

- Whole blood sample for virology
- Review of adverse events and concomitant medications

Subjects will be screened within 30 days before study entry to determine eligibility for participation in the study.

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 of the study.

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 electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Visit

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 evaluations before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after this 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, including weight
- Obtain blood and urine samples as described in sections 6.9 and 6.10

  — $eGFR_{CG}$

- Cystatin-C
- Whole blood sample for virology
- Patient reported outcomes: Subject is to read questionnaires by her/himself and write/mark answers directly onto questionnaires prior being administered study drug.
  - Visual Analog Scale (VAS)
  - HIV Treatment Satisfaction Status (HIVTSQs)
  - EQ-5D
  - Short Form 36 Health Survey (SF-36)
  - Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- Dispense study drug
- Subjects must initiate dosing of study drug or current regimen within 24 hours after the Day 1 visit.
- Subjects should also be counseled regarding the importance of adherence and taking their study drug once daily at approximately the same time each day

6.3. Treatment Assessments

6.3.1. Treatment Visits (Weeks 4-96)

The following assessments are to be completed at the end of Weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96 unless otherwise specified.

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 2 days of the visit date through Week 12 and completed within ± 6 days of the visit date through Week 96. The visit window at Week 24, Week 48, Week 72 and Week 96 may be ± 6 weeks of the visit date, if notified by Gilead. Unless notified by Gilead, the Week 24, Week 48, Week 72 and Week 96 visits should be completed within ± 6 days of the visit date.

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 (all visits)
- Complete physical examination (Weeks 48 and 96) (urogenital/anorectal exams will be performed at the discretion of the Investigator)

- Symptom-directed physical examination (Weeks 4, 12, 24, 36, 60, 72, and 84)
- Vital signs measurement, including weight (all visits)
- 12-lead ECG (Weeks 48 and 96 only)
- Obtain blood and urine samples as described in Sections 6.9 and 6.10
  - $eGFR_{CG}$ (all visits)
- Subjects who meet the criteria for virologic rebound should be managed according to Section 6.12, Virologic Failure
- HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 200 copies/mL (Weeks 48, 72 and 96 only)
- Patient reported outcomes: Subject is to read questionnaires by her/himself and write/mark answers directly onto questionnaires.
  - Visual Analog Scale (VAS) (all visits)
  - HIV Treatment Satisfaction Change (HIVTSQc) (Weeks 4, 24, and 48)
  - EQ-5D (Weeks 24 and 48)
  - SF-36 (Weeks 24 and 48)
  - FACIT-F (Weeks 24 and 48)
- Document study drug dispensation and accountability for B/F/TAF study drug (all visits)

6.4. Treatment Assessments (Post Week 96 extension phase)

At the Week 96 Visit, subjects in a country where B/F/TAF FDC is not yet commercially available will be given the option to receive B/F/TAF FDC for up to additional 48 weeks (up to week 144) and attend study visits every 12 weeks, 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 B/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 96 extension phase will be required to return for study visits according to the schedule present in Appendix 2 and described in the text below:

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

- Vital signs measurement, including weight
- Obtain blood and urine samples as described in Sections 6.9 and 6.10
  - eGFR$_{CG}$ (all visits)
- Subjects who meet the criteria for virologic rebound should be managed according to Section 6.12, Virologic Failure
- Document study drug dispensation and accountability

6.4.1. Early Study Drug Discontinuation Visit

If a subject discontinues study drug prior to Week 96, the subject will be asked to return to the clinic within 72 hours for the ESDD visit. The subject will be asked to continue attending the scheduled study visits through Week 96.

If a subject discontinues study drug before the completion of post Week 96 extension phase, the subject will be asked to return to the clinic within 72 hours for the ESDD Visit.

Subjects who complete the study drug through Week 96, and who do not continue participation in the post Week 96 extension phase, will not be required to complete the Early Study Drug Discontinuation Visit.

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

The following evaluations are to be completed at this 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, including weight
- 12-lead ECG
- Obtain blood and urine samples as described in Sections 6.9 and 6.10
  - eGFR$_{CG}$
- Patient reported outcomes: Subject is to read questionnaire by her/himself and write/mark answers directly onto questionnaire.
  - VAS
  - HIVTSQc

- HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 200 copies/mL

- Document study drug accountability

6.4.2. 30 Day Follow-Up Visit

- For subjects discontinuing study between Day 1 – Week 96

  If the subject discontinues study drug and does not continue in the study, the subject will be required to return to the clinic 30 days after the completion of the Early Study Drug Discontinuation Visit for the 30-Day Follow-Up visit.

  If the subject discontinues study drug and continues in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit, the subject will not be required to complete the 30-Day Follow-Up Visit.

  If the subject completes the study drug through Week 96 and does not continue participation in the post Week 96 extension phase, the subject will be required to return to the clinic 30 days after the completion of study drug for the 30-Day Follow-Up visit.

- For subjects discontinuing study post Week 96 extension phase

  If the subject discontinues study drug before the completion of post Week 96 extension phase, the subject will be required to return to the clinic 30 days after the completion of the Early Study Drug Discontinuation Visit for the 30-Day Follow-Up visit

  If the subject continues participation in the extension phase post Week 96, the subject will be required to return to the clinic 30 days after the completion of the extension phase for the 30-Day Follow-Up visit.

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

- Review of AEs and changes in concomitant medications

- Symptom-directed physical examination

- Vital signs measurement, including weight

- Obtain blood and urine samples as described in Sections 6.9 and 6.10

At the 30 Day Follow-Up 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.

6.5. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.6, 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.

6.6. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

- Development of active tuberculosis infection
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Lack of efficacy
- Subject request to discontinue for any reason

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.
- 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)

6.7. End of Study

End of study is defined as completion of the 96 weeks of treatment and the 30 Day Follow-Up visit. Subjects that enter the post Week 96 extension phase will have the week 96 study visit, then up to 48 weeks on the extension phase and the 30 Day Follow-Up visit.

6.8. 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.

6.9. Blood Samples

Blood sample collection for the following laboratory analyses:

- Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, sodium (all visits)
- Hematology profile: complete blood count (CBC) with differential and platelet count (all visits)
- CD4+ cell count (all visits)
- Plasma HIV-1 RNA (TaqMan® v2.0) (all visits)
- Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb). The following tests will be conducted by the central laboratory if the following criteria are met (Screening visit)
  - If positive HBsAg: reflex testing for plasma HBV DNA, Hepatitis B virus e-antigen (HBeAg) (if negative, reflex Hepatitis B virus e-Antibody [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 (HCV Ab) serology (reflex HCV RNA is performed in subjects with positive HCV Ab serology) (Screening Visit)
- Metabolic assessments: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) (Day 1, Weeks 24, 48 and 96); metabolic assessments will not be collected after Week 96.
- 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.
- Biomarkers to be analyzed may include but will not be limited to: soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer (Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96); Biomarkers will not be collected after Week 96. A portion of the biomarker blood sample obtained at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96 may be utilized to assess study drug PK. This will be a random sample with the date and time of the subject's last medication dose recorded.

- Inflammation evaluations may include: cystatin-C, IL 6, hs CRP, sCD14, sCD163, sTNF-R1, and Lp-PLA2. Specimens will be collected from all subjects (Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96). Inflammation markers will not be collected after Week 96.

- Plasma storage sample for safety and/or virology testing (all visits)

- Whole blood sample for virology (Screening and Day 1)

6.10. Urine Samples

Urine collection for the following laboratory analyses:

- Urinalysis (all visits)

- Urine chemistry (all visits)

- Renal safety evaluations: Fasting (no food or drink, except water, at least 8 hours prior to blood collection) retinol binding protein and beta-2 microglobulin (Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96). Renal safety evaluations will not be done after Week 96.

6.11. Blood and Urine Sample Storage

Residual blood and urine samples taken throughout the study (including the post Week 96 extension phase) 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. These samples will be stored until the completion of all visits for all subjects and the final study analysis.

6.12. Virologic Failure

Virologic failure is defined as confirmed virologic rebound of HIV-1 RNA ≥ 50 copies/mL at 2 consecutive visits, or having HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation or at Week 48, Week 72 or Week 96.

6.12.1. 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

Following the virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (within 2-3 weeks after the date of the original test that resulted in HIV-1 RNA ≥ 50 copies/mL). Subjects with HIV-1 RNA values between 50-200 copies/mL should follow the algorithm in Figure 6-1. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing.

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.

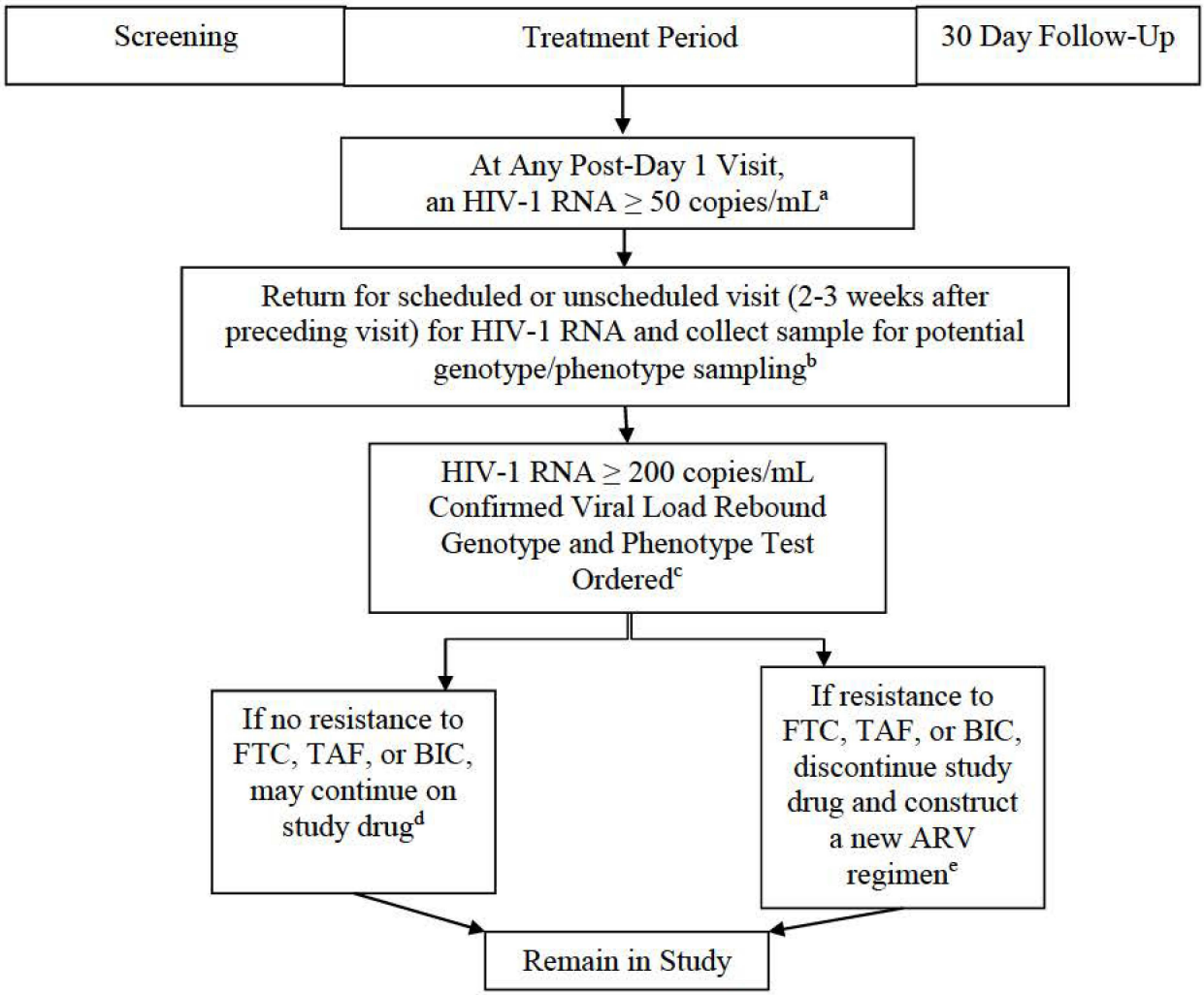
If no resistance to study drugs is detected from the genotype or phenotype, the subject may remain on study drugs and HIV-1 RNA test should be analyzed at a new visit (within 2-3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of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

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

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

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

Figure 6-1. Virologic Rebound Schema



a If the HIV-1 RNA is between 50 and 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma if available. If the repeat result is < 50 copies/mL, then no further action is required. If the repeat result is ≥ 50 copies/mL then proceed to the scheduled or unscheduled visit 2 – 3 weeks later.

b If the HIV-1 RNA is < 50 copies/mL then no further action is required. If the HIV-1 RNA is between 50 and 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma if available. If the repeat result is < 50 copies/mL, then no further action is required. If the repeat result is between 50 and 200 copies/mL this is protocol defined confirmed virologic failure and the Medical Monitor should be consulted. If the repeat result is ≥ 200 copies/mL, then a Genotype and Phenotype test will be ordered.

c If virologic rebound is confirmed and the last HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed. If the genotype and phenotype assay fails, Investigator reviews study drug continuation/discontinuation options and discuss with the Medical Monitor prior to study drug discontinuation.

d If no resistance to study drug is detected, HIV-1 RNA will be repeated 2 – 3 weeks later. Investigator reviews study drug continuation/discontinuation options and discuss with the Medical Monitor prior to study drug discontinuation. The subject will remain in the study.

e A new ARV regimen will be configured, at the Investigator's discretion and the subject will remain in the study.

6.12.2. Subjects with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation or at Week 48, Week 72 or Week 96

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 Weeks 48, 72 or 96 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 last measurement in the Weeks 48, 72 or 96 window, 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
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

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

7.1.3. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the 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 (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

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

7.1.4. Assessment of Severity

AE severity should be recorded and graded according to the Gilead 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.

7.2. 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.

7.2.1. 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.

7.2.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PV&E) 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 PV&E.

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

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PV&E 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 report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead PV&E: Fax: PPD
E-mail: PPD

- 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.

- 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.

- 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 and the event description section of the SAE form.

7.3. Gilead Reporting Requirements

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

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

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

7.4. Toxicity Management

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

Refer to Section 6.6, Criteria for Study Drug Interruption or Discontinuation, for additional specific discontinuation criteria. For Specific toxicity discontinuation criteria please refer to Section 7.4. The Gilead Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

7.4.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.4.2. Grades 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinically significant laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to IMP, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation.

7.4.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality that is considered related to IMP, IMP should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 creatine kinase [CK] after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed)

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

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

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

A 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

7.4.4.1. 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.

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

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

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.
- Check the following laboratory parameters: serum ALT and AST, bilirubin, INR, and albumin.
- If the ALT elevation is confirmed, request the clinical laboratory to conduct reflex testing for plasma HBV DNA, HBV serology (HBsAg and HBsAb), HDV, HAV IgM and HCV. If serum HBV DNA is increasing, the investigator should consider immediate initiation of approved therapy.
- The subject should be followed until laboratory parameters (ALT, total bilirubin, INR) return to normal or Day 1 up to a maximum of 6 months after the initial occurrence of the event.

7.4.5. Management of Potential Hepatobiliary Toxicity

Monkeys given a high dose (1000 mg/kg/day) for 39 weeks had evidence of biliary hyperplasia and hepatocyte hypertrophy on histopathologic examination. The risk to humans given the clinical dose of bictegravir (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 7.4.

7.4.6. 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. Study drug may be continued without dose interruption. Should the Investigator decide to initiate Hepatitis C treatment, the Investigator must contact the Gilead Medical Monitor to confirm that no drug-drug interactions with Hepatitis C medications are expected. Subjects should return to the clinic for scheduled or unscheduled follow up visit(s) according to local medical practice for laboratory evaluations. If Hepatitis C treatment is initiated, Investigators should use the Gilead provided retest laboratory kits to manage the active Hepatitis C.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

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

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

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

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

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

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

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

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Reporting Special Situations

All special situation reports must be reported on the special situations report form and forwarded to Gilead PV&E within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

Gilead PV&E contact information is as follows:

Email: PPD and
Fax: PPD

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

- To characterize the virologic efficacy of switching virologically suppressed subjects on an E/C/F/TAF FDC or TDF-containing regimen (if currently or previously participated in GS-US-292-1826) to B/F/TAF FDC defined by HIV-1 RNA <50 copies/mL at Week 24.
- The secondary objectives of the study are to characterize the safety and tolerability of switching to B/F/TAF FDC from an E/C/F/TAF FDC or TDF-containing regimen (if currently or previously participated in GS-US-292-1826) and to characterize the virologic efficacy of switching to B/F/TAF FDC defined by HIV-RNA <50 copies/mL at Week 48, Week 72, and Week 96.

8.1.2. Primary Endpoint

The primary endpoint is HIV-1 RNA <50 copies/mL at Week 24 as defined by the Food and Drug Administration (FDA) snapshot algorithm

8.1.3. Secondary Endpoints

Secondary endpoints to be evaluated are

- adverse events through Week 24
- adverse events through Week 48
- adverse events through Week 72
- adverse events through Week 96
- HIV-1 RNA <50 copies/mL at Week 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm
- HIV-1 RNA <50 copies/mL at Week 72 as defined by the Food and Drug Administration (FDA) snapshot algorithm
- HIV-1 RNA <50 copies/mL at Week 96 as defined by the Food and Drug Administration (FDA) snapshot algorithm

8.1.4. Other Endpoints of Interest

Other endpoints of interest are:

- Subject satisfaction after switching to B/F/TAF FDC
- Number of potentially interacting medications

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all subjects who received at least one dose of study drug.

All data collected during treatment up to 30 days after the last dose of study drug will be included in the safety summaries**.**

8.2.1.3. Biomarkers

All subjects with available biomarkers data will be included in the Biomarker dataset.

8.3. Data Handling Conventions

In general, baseline value is defined as the last value measured on or prior to Day 1 of the study.

8.4. Demographic Data and Baseline Characteristics

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

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

Baseline data will include a summary of body weight, height, body mass index, risk factors for HIV-1 infection, and background HIV therapy at study entry (E/C/F/TAF vs TDF containing regimen).

8.5. Efficacy Analysis

The proportion of subjects maintaining HIV-1 RNA < 50 copies/mL (as defined by the FDA snapshot analysis) at Week 24 and its 95% confidence interval will be estimated. Additionally, the 95% CI for the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL (per snapshot analysis) at Week 24 will be calculated and presented.

Similar summary tables will be provided to characterize the efficacy of study drug at Week 48, Week 72, and Week 96.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to 30 days after the date of last dose of IMP will be summarized. Data for the pretreatment period and post the date of last dose plus 30 days will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to ~~s~~study drug will be generated from the IMP administration data. Exposure data will be summarized.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration, and summarized. Dosing information for individual subjects will be listed.

8.6.2. 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, and PT) will be provided. Additional summaries may include summaries for adverse events by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme 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. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum post baseline toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of IMP or after the subject has been discontinued from treatment for 30 days will be included in a data listing.

8.7. Sample Size

The sample size is based on feasibility of conducting a study with ≥65 year old subjects.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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

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

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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/IEC or local requirements.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, CRF and query forms, 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, 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 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 IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

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

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

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.2.2).

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

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

European AIDS Clinical Society (EACS). European AIDS Clinical Society (EACS) Guidelines Version 8.2 January, 2017.

Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. A Phase 3 Randomized Controlled Clinical Trial of Bictegravir in a Fixed Dose Combination, B/F/TAF, vs DTG/ABC/3TC in Treatment-Naïve Adults at Week 48 [Presentation W48]. 9th IAS Conference on HIV Science; 2017 23–26 July; Paris, France.

Gallant J, Thompson M, DeJesus E, Voskuhl G, Wei X, Zack J, et al. Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients [Poster PW-030]. ASM Microbe; 2016 16-20 June; Boston, MA.

Gilead Sciences Inc. Gilead's Investigational Fixed-Dose Combination of Bictegravir, Emtricitabine and Tenofovir Alafenamide for the Treatment of HIV-1 Meets Primary Endpoint in Four Phase 3 Studies. *U.S. NDA Submission Planned for Q2 2017; EU MAA Filing Planned for Q3 2017*. 2017.

Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352 (9142):1725-30.

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining Morbidity and Mortality Among Patients With Advanced Human Immunodeficiency Virus Infection. N Eng J Med 1998;338 (13):853-60.

Sax PE, Pozniak A, Arribas J, Koenig E, DeJesus E, Stellbrink HJ, et al. Phase 3 Randomized, Controlled, Clinical Trial of Bictegravir Coformulated With FTC/TAF in a Fixed-Dose Combination vs Dolutegravir + FTC/TAF in Treatment-Naïve HIV-1-Positive Adults: Week 48 Results [Poster TUPDB0201LB]. 9th IAS Conference on HIV Science; 2017 23–26 July; Paris, France.

Selik RM, Mokotoff ED, Branson B, Owen SM, Whitmore S, Hall HI. Morbidity and Mortality Weekly Report (MMWR). Revised Surveillance Case Definition for HIV Infection - United States 2014. Centers for Disease Control and Prevention, 2014.

Sterne J, Hernán M, Ledergerber B, Tilling K, Weber R, Sendi P, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005;366 (9483):378-84.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient preference and adherence 2012;6:427-33.

UNAIDS. Fact Sheet 2016: Global Statistics-2015. Available at: http://www.unaids.org/en/resources/documents/2016/UNAIDS_FactSheet. 2016.

11. APPENDICES

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Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching from an Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Regimen or a Tenofovir Disoproxil Fumarate Containing Regimen to Fixed-Dose Combination of Bictegravir /Emtricitabine/Tenofovir Alafenamide in Elderly, Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 65 Years

GS-US-380-4449 Amendment 2, 18 December 2018

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

PPD

PPD

18 DEC 2018
Date

PPD

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]									Post Week 96 extension phase	Early Study Drug Discontinuation (ESDD)[d]	30-Day Follow-up
			4	12	24	36	48	60	72	84	96	Every 12 weeks for 48 weeks (until Week 144)		
Informed Consent	X													
Medical History	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X	X					X				X		X	
Symptom-Directed Physical Exam			X	X	X	X		X	X	X		X		X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
12-lead ECG	X						X				X		X	
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]
Renal Safety Evaluations – Urine[f]		X	X	X	X		X	X	X	X	X			
Biomarkers: inflammation, platelet, renal[g]		X	X	X	X		X	X	X	X	X			
Urine Storage Sample		X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma HIV-1 RNA[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HBV and HCV Serologies[k]	X													
Cystatin-C		X												
Estimated GFRCGl	X	X	X	X	X	X	X	X	X	X	X	X	X	
Whole Blood Sample[m]	X	X												

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]									Post Week 96 extension phase	Early Study Drug Discontinuation (ESDD)[d]	30-Day Follow-up
			4	12	24	36	48	60	72	84	96	Every 12 weeks for 48 weeks (until Week 144)		
Metabolic Assessments[n]		X			X		X				X			
Plasma Storage Sample[o]		X	X	X	X	X	X	X	X	X	X	X	X	
Patient reported outcomes: VAS		X	X	X	X	X	X	X	X	X	X		X	
Patient reported outcome: HIVTSQs		X												
Patient reported outcome: HIVTSQ[c]			X		X		X						X	
Patient reported outcome: EQ-5D		X			X		X							
Patient reported outcome: SF-36		X			X		X							
Patient reported outcome: FACIT-F		X			X		X							
HIV-1 Genotype/Phenotype[q]							X		X		X		X	
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X	X	X	X	X[r]	

a Evaluations to be completed within 30 days prior to Day 1 visit.

b Subjects will be dispensed study drug at the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 6 days of the protocol specified date through Week 96. The Week 24, 48 and 96 visits window is ± 6 weeks of the visit date, if notified by Gilead. Unless notified by Gilead, the Week 24,, 48 and 96 visits should be completed within ± 6 days of the visit date. 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.

d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 96 visit even as the subject discontinues study drug.

e Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator).

f Urine for renal safety, including retinol binding protein, and beta-2-microglobulin, will be collected. Samples for renal safety will be collected fasted. 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.

g Inflammation may include cystatin-C, IL-6, hs-CRP, sCD14, sCD163, sTNF-1R, and Lp-PLA2; Platelet and coagulation function may include soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer will be collected. Urine for renal safety, including retinol binding protein, and beta-2-microglobulin, will be collected. Samples for renal safety will be collected fasted. 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. A portion of the biomarker blood sample obtained at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84 and 96may be utilized to assess study drug PK. This will be a random sample with the date and time of the subject's last medication dose recorded.

h Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium. At Day 1, Weeks 24, 48 and 96 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

i CBC with differential and platelet count.

j For the management of virologic rebound please refer to section 6.12.

k Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb).

l Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance.

m Whole blood sample for virology analysis.

n Metabolic Assessments: Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state.

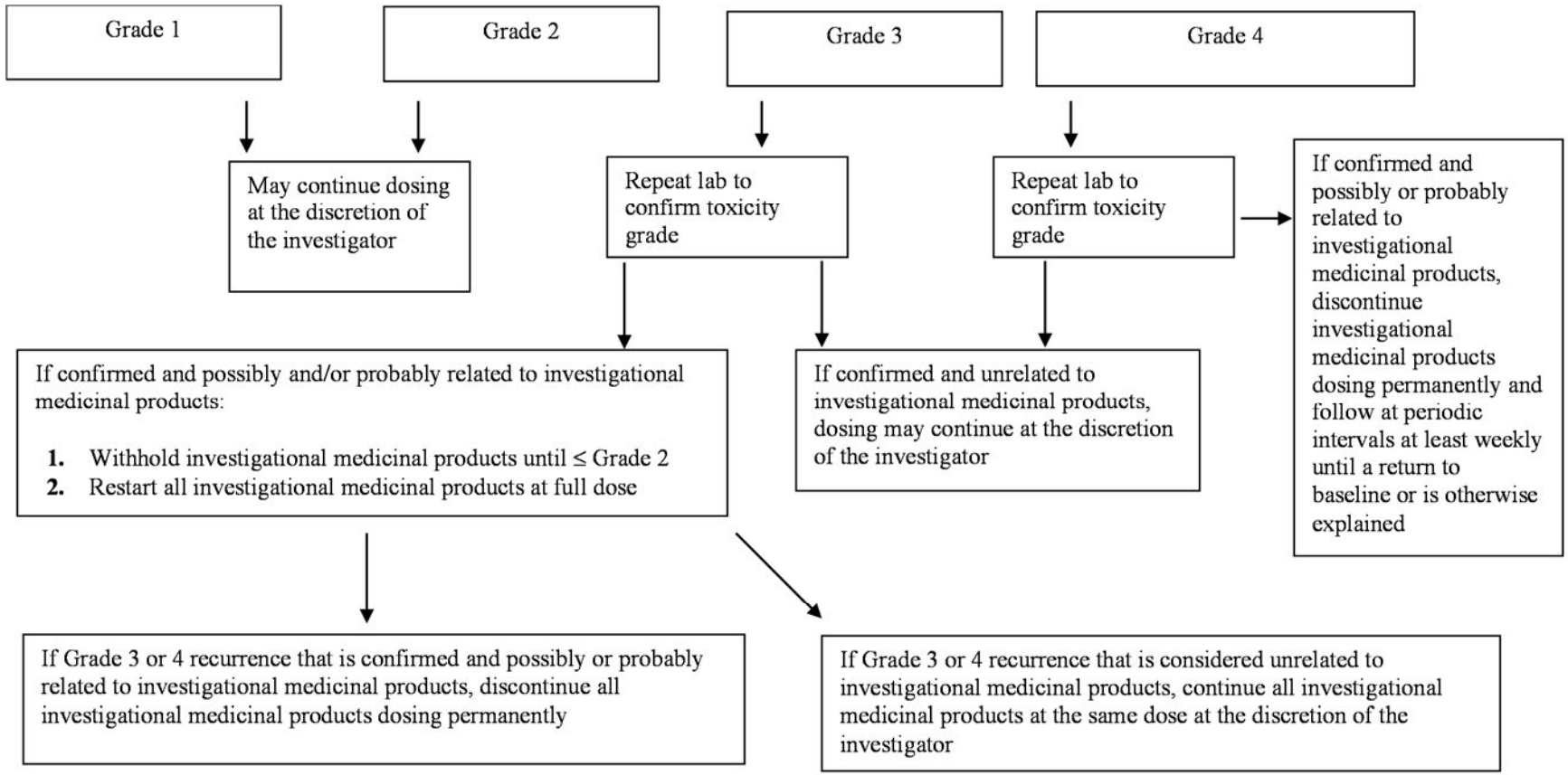
o Plasma storage sample for safety and/or virology (Day 1, Weeks 4-96, and ESDD).

p Urinalysis only.

q The geno/pheno is only done if the last HIV-1 RNA is > 200 copies/mL.

r Drug accountability only; study drug will not be dispensed at this visit.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL	> 11.5 to 12.5 mg/dL	> 12.5 to 13.5 mg/dL	> 13.5 mg/dL
	>ULN to 2.88 mmol/L	> 2.88 to 3.13 mmol/L	> 3.13 to 3.38 mmol/L	> 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL	> 6.0 to 6.5 mg/dL	> 6.5 to 7.0 mg/dL	> 7.0 mg/dL
	> ULN to 1.50 mmol/L	> 1.50 to 1.63 mmol/L	> 1.63 to 1.75 mmol/L	> 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L	< 0.67 mg/dL < 0.6 mEq/L
	0.58 to <LLN mmol/L	0.43 to < 0.58 mmol/L	0.28 to < 0.43 mmol/L	< 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL	> 10.0 to 12.0 mg/dL	> 12.0 to 15.0 mg/dL	> 15.0 mg/dL
	>ULN to 597 µmol/L	> 597 to 716 µmol/L	> 716 to 895 µmol/L	> 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[**]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN	11.0 to < 16.0 mEq/L	8.0 to < 11.0 mEq/L	< 8.0 mEq/L
Adult and Pediatric ≥ 4 Years	16.0 mmol/L to < LLN	11.0 to < 16.0 mmol/L	8.0 to < 11.0 mmol/L	< 8.0 mmol/L

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

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 Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

Male subjects must agree to refrain from sperm donation from first study drug dose until after the end of relevant systemic exposure.

3) Unacceptable Birth Control Methods

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

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

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

23. *Salmonella* septicemia, recurrent

24. Toxoplasmosis of brain

25. Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Selik 2014}