CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching From a Regimen of Two Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI) plus a Third Agent to a Fixed Dose Combination (FDC) of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF), in Virologically-Suppressed, HIV-1 Infected African American Participants	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside drive Foster City, CA 94404	
IND Number:	125,589	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	Not Available	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-380-4580	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
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Protocol Version/Date:	Original:	27 June 2018

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching From a Regimen of Two Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI) plus a Third Agent to a Fixed Dose Combination (FDC) of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF), in Virologically-Suppressed, HIV-1 Infected African American Participants
IND Number:	125,589
EudraCT Number:	NA
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Multiple centers in the United States
Objectives:	The primary objective of this study is: • To evaluate the efficacy of switching from a regimen of 2 NRTIs and a third agent to a fixed dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing their baseline regimen in HIV-1 infected, virologically suppressed African American participants as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 The secondary objectives of this study are: • To evaluate the efficacy of switching to a FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 • To evaluate the efficacy, safety, and tolerability of switching to FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent in HIV-1 infected, virologically suppressed African American participants through Week 48

Study Design:	Randomized, open-label, multicenter, active-controlled study of HIV-1 infected, virologically suppressed African American participants. Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups: **Treatment Group 1 (n=320):** FDC of B/F/TAF (50 mg/ 200 mg/ 25 mg) administered orally, once daily (QD), without regard to food. **Treatment Group 2 (n=160):** Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, QD, without regard to food at Week 24. Randomization will be stratified by the baseline 3rd agent ARV class at entry (integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or CCR5 antagonist). Study duration will be at least 48 weeks in this study.
Number of Participants Planned:	Approximately 480 participants
Target Population:	HIV-1 infected adult participants that self-describe as Black, African American, or mixed race, including Black, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of two NRTIs and a 3rd agent for ≥ 6 months prior to screening
Duration of Treatment:	After screening, eligible participants will be treated for at least 48 weeks. Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants randomized to SBR will have, after their delayed switch, an additional visit at Week 28. Participants who complete the study through the Week 48 visit and wish to continue on FDC of B/F/TAF, will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and will attend study visits every 12 weeks followed by a 30-Day Follow-Up Visit. Participants who complete the study through the Week 48 Visit and do not continue their participation in the study, will be required to return to the clinic 30 days after their Week 48 Visit for a 30-Day Follow-Up Visit.

Diagnosis and Main Eligibility Criteria:

Participants must meet all of the following inclusion criteria to be eligible to participate in the study. Eligible participants with chronic hepatitis C virus (HCV) infection are permitted to enroll. In addition, eligible participants with chronic hepatitis B virus (HBV) infection are permitted to enroll if their baseline regimen contains either TAF or TDF.

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

- Self-describes as Black, African American, or mixed race, including Black
- Currently receiving an ARV regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed 3rd agent for ≥ 6 months
  - Allowed 3rd agents include any FDA-approved INSTI, with the exception of bictegravir, any FDA-approved NNRTI with the exception of etravirine, PI or the CCR5 antagonist, maraviroc.
  - If the baseline 3rd agent is dolutegravir, dosing other than 50 mg once daily is excluded.
  - Baseline regimens containing investigational drugs or > 2 classes of ARVs are not permitted, with the exception of the pharmacologic enhancers cobicistat (taken with elvitegravir or a PI), or ritonavir (taken with a PI).
- Have no documented or suspected resistance to INSTIs and no history of virologic failure on an INSTI containing regimen (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving <50 copies/mL while on an INSTI-containing regimen).
- History of 1-2 thymidine analogue mutations (TAMs), M184V/I, and any other RT substitutions are allowed, with the following exceptions: History of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT will be excluded.
- Documented plasma HIV-1 RNA < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months and at least the last two HIV-1 RNA measurements prior to the Screening visit
- HIV-1 RNA levels < 50 copies/mL at Screening
- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance

Study Procedures/ Frequency:	After Screening procedures, eligible participants will be randomized 2:1 to Treatment Group 1 or Treatment Group 2 and treated for 48 weeks. Following the Day 1 visit, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants randomized to SBR will have an additional visit at Week 28. 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 Screening, Day 1 and subsequent study visits. Whole blood for HIV-1 DNA archive testing will be collected at Day 1 for all participants and at Week 24 for all participants in Treatment Group 2. Historical HIV-1 RNA genotypes will be collected if available.
Test Product, Dose, and Mode of Administration:	FDC of bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food
Reference Therapy, Dose, and Mode of Administration:	Baseline regimen consisting of 2 NRTIs and an allowed 3rd agent taken as prescribed
Criteria for Evaluation:	
Safety:	Adverse events, clinical laboratory tests, and tolerability of treatment regimens
Efficacy:	The primary efficacy endpoint is: • The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as defined by the US FDA-defined snapshot algorithm The secondary efficacy endpoints are: • The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm • The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 and 48 as defined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ cell count at Weeks 24 and 48.

Patient reported outcomes:	HIV Symptoms Distress Module Index will be administered at Day 1, Weeks 4, 24, 28 (SBR only) and 48. HIV Treatment Satisfaction Questionnaire Status (HIV-TSQs) will be administered at Day 1 and HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc) will be administered at Week 4 and Week 24. Visual Analogue Scale (VAS) Adherence Questionnaire will be administered at Day 1 and at all visits up to (and including) Week 24 for participants in Treatment Group 2 (SBR) only.
Statistical Methods:	The primary analysis will consist of a non-inferiority test of switching to FDC of B/F/TAF versus SBR, with respect to the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24, as defined by the US FDA-defined snapshot algorithm. It will be concluded that FDC of B/F/TAF is non-inferior to SBR if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment groups [B/F/TAF – SBR] in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL is less than 6% (i.e., a margin of 6% is applied to non-inferiority assessment). The 2-sided 95% CIs will be constructed based on the exact method. The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48, and the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be summarized. The 95% CIs at Week 24 will be constructed in the same manner as described for the primary efficacy endpoint. The change from baseline in CD4+ cell count at Weeks 24 and 48 will be summarized by treatment using descriptive statistics. The differences and the associated 95% CIs at Week 24 will be constructed using an Analysis of Variance (ANOVA) model, including treatment (B/F/TAF vs. SBR). Adverse events and clinical laboratory assessments will be summarized using descriptive statistics. Sample sizes of 320 in B/F/TAF FDC and 160 in SBR Group achieve approximately 89% power to detect a non-inferiority margin difference between the group proportions of 0.06 for HIV-1 RNA ≥ 50 copies/mL at Week 24. The assumed reference group proportion is 0.04. The treatment group proportion is assumed to be 0.10 under the hypothesis of inferiority. The power is computed for the case when the actual treatment group difference is zero (treatment = reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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

F/TAF	emtricitabine/tenofovir alafenamide , Descovy®
F/TDF	emtricitabine/tenofovir disoproxil fumarate, Truvada®
FSH	follicle-stimulating hormone
FTC, F	emtricitabine, Emtriva®
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GLSM	geometric least squares mean
GSI	Gilead Sciences, Inc.
GS-9883	bictegravir, B
GS-9883/F/TAF	GS-9883/emtricitabine/tenofovir alafenamide
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e-antibody
HBeAg	hepatitis B e-antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
HCC	hepatocellular carcinoma
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HIV Sx	HIV Symptoms Distress Module
HIV	HIV Treatment Satisfaction Questionnaire
HIV-TSQs	HIV Treatment Satisfaction Questionnaire Status
HIV-TSQc	HIV Treatment Satisfaction Questionnaire Change
HLA	human leukocyte antigen
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INSTI	integrase strand-transfer inhibitors
IRB	institutional review board
IWRS	interactive web response system
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

MH	Mantel-Haenszel
min	Minute
mmHg	millimeters mercury
nM	nanoMolar
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOEL	no observed effect level
OL	Open Label
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PEP	post-exposure prophxylaxis
P-gp	P-glycoprotein
PI	protease inhibitor
PK	Pharmacokinetic
PT	preferred term
PT	prothrombin time
PTM	placebo-to-match
PVE	Pharmacovigilance and Epidemiology
QD	once daily
RAL	Raltegravir
RNA	ribonucleic acid
SA	single agent
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide
TAM	thymidine analogue mutation
TDF	tenofovir disoproxil fumarate, Viread®
TFV-DP	tenofovir diphosphate (TFVpp)
t_{max}	the time (observed time point) of C_{max}
TSH	thyroid stimulating hormone
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.4 million people in North America and Western and Central Europe living with HIV-1 and 37 million people worldwide {Joint United Nations Programme on HIV/AIDS (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}.

With the success of potent and well-tolerated antiretroviral therapy (ART) clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}.

For ART-naive HIV-infected patients, current treatment guidelines recommend that initial therapy for most people consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and an integrase strand-transfer inhibitor (INSTI) {Panel on Antiretroviral Guidelines for Adults and Adolescents 2018}.

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

Gilead Sciences (Gilead) has coformulated BIC with the NRTI emtricitabine (FTC; F) and the NtRTI TAF into a fixed dose combination (FDC) tablet that is suitable for once daily use. This bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) FDC provides a potent, convenient, tolerable, and practical regimen for the long term treatment of patients with HIV infection. B/F/TAF (Biktarvy®) was approved for the treatment of adults with HIV-1 infection by the FDA and is recommended in DHHS treatment guidelines.

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 FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Sterrantino 2012}, {Aldir 2014}. Virologically suppressive ART has also contributed to a decline in HIV incidence in communities with high rates of virologic suppression, by reducing the transmissibility of infected individuals on treatment {Grabowski 2017}, {Kurth 2011}.

In the US, not all communities have benefitted equally from advancements in HIV treatment. African Americans remain disproportionately affected by the epidemic. The prevalence of HIV is 8 fold higher in African Americans compared to whites and disparities in the risk for HIV acquisition are magnified in African American women whose risk is 16 times that of white women. The prognosis of living with HIV is also worse for African Americans for whom the risk of death from HIV disease is approximately nine times that of their white counterparts {Centers for Disease Control and Prevention (CDC) 2018}.

Racial inequities in access to medical care, medical insurance and in trust in the medical system are well documented in US healthcare, as are racial differences in clinical outcomes {Bailey 2017}. Structural and interpersonal discrimination influence not only who has access to the medical system, but also determine the care they receive from physicians. Amongst persons living with HIV who are engaged in medical care, race, gender, and geographic differences influence physician prescribing patterns for ARVs and prophylactic medications {Lemly 2009}, {King 2008}, {Meditz 2011}, {Oramasionwu 2011}, {Oramasionwu 2012}. Since the US social factors and structural inequalities confounding health disparities are poorly measured, even large sophisticated studies may not rule out the possibility that biological differences contribute to these disparities in clinical outcomes {Ribaudo 2013}. This has complicated clinical decision making despite evidence that race and ethnic origin play no major role in outcomes associated with HAART where access to health care is more equitably distributed {Jensen-Fangel 2002}.

1.2. Bictegravir (GS-9883, B)

1.2.1. General Information

Bictegravir, a potent inhibitor of HIV-1 integrase is now approved for the treatment of HIV infection.

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. Please refer to the Investigator Brochure for details.

1.2.2.1. Pharmacology

Bictegravir is absorbed following oral administration with peak plasma concentrations occurring at 2-4 hours after administration. The multiple dose pharmacokinetics of BIC are dose proportional over the dose range of 25 to 100 mg Relative to fasting conditions, administration with either a moderate fat (~600 kcal, 27% fat) or high fat meal (~800 kcal, 50% fat) resulted in an increase in BIC AUC (24%). This modest change is not considered clinically meaningful and BIC can be administered with or without food.

Bictegravir is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and 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.

BIC is primarily eliminated by hepatic metabolism. Renal excretion of intact BIC is a minor pathway (~1% of dose). The plasma BIC half-life was 17.3 hours.

1.2.2.2. Toxicology

The nonclinical safety profile of BIC has been well characterized in genetic toxicology, safety pharmacology (central nervous system [CNS], cardiovascular [CV], respiratory), carcinogenicity, repeat-dose toxicity, and developmental toxicity studies. Bictegravir is not genotoxic and did not have adverse effects on the CNS, CV, or respiratory systems. Bictegravir demonstrated no carcinogenic potential in 6-month transgenic mouse or 2-year rat carcinogenicity studies at exposures 15- or 31-fold higher, respectively, than the estimated clinical exposure of BIC when administered as B/F/TAF (50/200/25 mg), hereafter referred to as exposure margins. The no-observed-adverse-effects levels (NOAELs) in chronic 26-week rat and 39-week monkey toxicity studies were at exposure margins of 18-/46-fold (males/females) and 7.0-fold, respectively. Administration of BIC to cynomolgus monkeys at a high dose of 1000 mg/kg/day for 39 weeks resulted in microscopic liver changes that persisted through the recovery phase; observed increased alanine aminotransferase (ALT) activities at 1000 mg/kg/day exhibited reversibility. In offspring from rat and rabbit dams treated with BIC during pregnancy, there were no toxicologically significant effects on developmental endpoints, and studies in animals administered BIC have shown no evidence of teratogenicity or an effect on reproductive function.

1.2.3. Clinical Trials of Bictegravir

Please refer to the B/F/TAF Investigators' Brochure for a list of clinical studies of BIC and B/F/TAF as well as 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 participants which helped establish the PK of BIC and evaluated the drug-drug interaction potential with F/TAF FDC. Please see the Investigator Brochure for additional details.

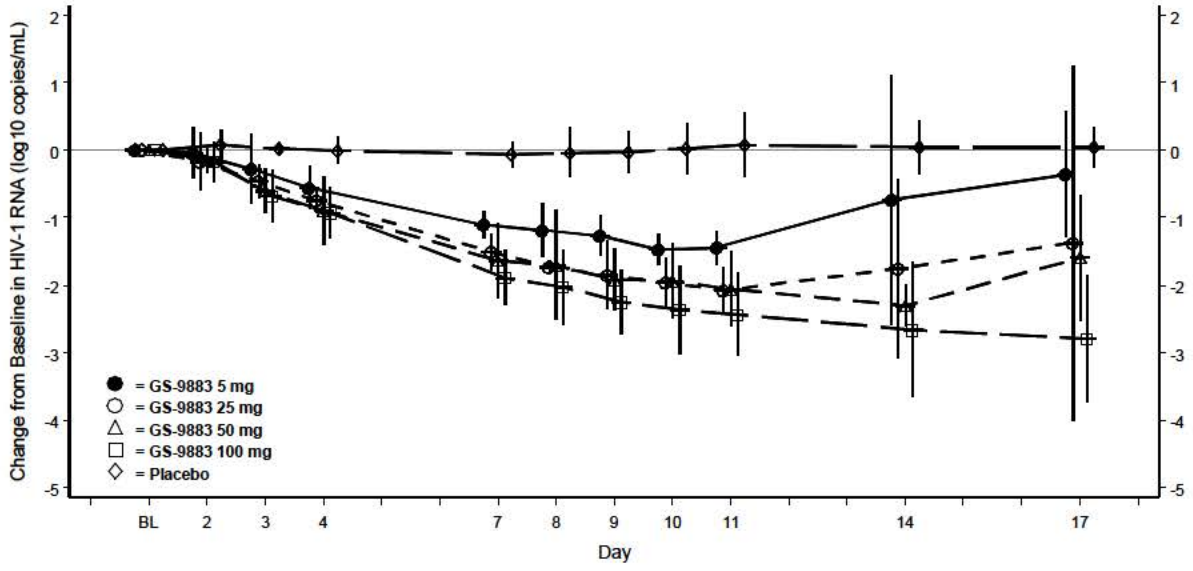
1.2.3.2. Phase 1b Proof of Concept

The first HIV-1 positive human participants were dosed in the fasted state with 10 days of bictegravir in study (GS-US-141-1219). Four cohorts of 5 participants 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.

There was no increase in the incidence of AEs with increasing doses of bictegravir.

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

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



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

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

Mean viral load change on Day 11 was -2.08 log_{10} in the 25 mg cohort, -2.06 log_{10} in the 50 mg cohort, and -2.43 log_{10} in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was -0.92 log_{10} in the 5 mg cohort, -1.33 log_{10} in the 25 mg cohort, -1.37 log_{10} in the 50 mg cohort and -1.61 log_{10} in the 100 mg cohort. Viral suppression (HIV-1 RNA < 50 copies/mL) was ever achieved by the end of the study (Day 17) by 1 participant (25.0%) in the bictegravir 50 mg group and 2 participants (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 B+F/TAF versus dolutegravir (DTG)+F/TAF in HIV-infected, ART-naive adult participants.

Eligible participants were randomized in a 2:1 ratio to receive BIC 75 mg + F/TAF (200/25 mg) + placebo-to-match DTG 50 mg once daily or DTG 50 mg + F/TAF (200/25 mg) + placebo-to-match bictegravir 75 mg once daily.

The primary efficacy endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm. The percentages of participants with HIV-1 RNA < 50 copies/mL at Week 24 was high in both groups, as follows: BIC+F/TAF 96.9%; DTG+F/TAF 93.9%; difference in percentages: 2.9%, 95% CI: −8.5% to 14.2%. Because the lower bound of the 95% CI for the difference in response rate (B+F/TAF – DTG+F/TAF) was greater than the prespecified −12% margin, B+F/TAF was determined to be noninferior to DTG+F/TAF.

HIV-1 RNA levels decreased rapidly in the first 4 weeks following initiation of study drug in both treatment groups. No resistance to any INSTIs, NRTIs, NNRTIs, or PIs was detected through Week 48 in the B+F/TAF group. Both B+F/TAF and DTG+F/TAF were generally well tolerated through 48 weeks of treatment with similar proportions of adverse events reported in each treatment group. Participants in both groups were switched to open-label B/F/TAF after all participants completed 48 Weeks of blinded treatment.

1.2.3.4. Summary of Phase 3 Studies

Treatment-Naïve Patients

In Study 1489, patients were randomized in a 1:1 ratio to receive either fixed-dose combination B/F/TAF (50/200/25 mg) (N = 314) or ABC/DTG/3TC (600/50/300 mg) (N = 315) once daily. In Study 1490, patients were randomized in a 1:1 ratio to receive either fixed-dose combination B/F/TAF (50/200/25 mg) (N = 320) or DTG + FTC/TAF (50+200/25 mg) (N = 325) once daily.

In Studies 1489 and 1490, the mean age was 35 years (range 18-77), 89% were male, 58% were White, 33% were Black, and 3% were Asian. 24% percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 log10 copies/mL (range 1.3-6.6). The mean baseline CD4+ cell count was 460 cells/mm3 (range 0-1636) and 11% had CD4+ cell counts less than 200 cells/mm^3. 18% of patients had baseline viral loads greater than 100,000 copies/mL. In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies/mL to less than or equal to 400,000 copies/mL, or greater than 400,000 copies/mL), by CD4 count (less than 50 cells/µL, 50-199 cells/µL, or greater than or equal to 200 cells/µL), and by region (US or ex-US).

Treatment outcomes of Studies 1489 and 1490 through Week 48 are presented in Table 1-1.

Table 1-1. Pooled Virologic Outcomes of Studies 1489 and 1490 at Week 48 in Treatment-Naïve Patients[a]

	B/F/TAF FDC (N = 634)[b]	ABC/DTG/3TC (N = 315)[c]	DTG + FTC/TAF (N = 325)[d]
HIV-1RNA < 50 copies/mL	91%	93%	93%
Treatment Difference (95% CI) B/F/TAF FDC vs. Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)
HIV-1 RNA ≥ 50 copies/mL[e]	3%	3%	1%
No Virologic Data at Week 48 Window	6%	4%	6%
Discontinued Study Drug Due to AE or Death[f]	<1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[g]	4%	3%	4%
Missing Data During Window but on Study Drug	2%	<1%	1%

a. Week 48 window was between Day 295 and 378 (inclusive).
b. Pooled from Study 1489 (N = 314) and Study 1490 (N = 320).
c. Study 1489
d. Study 1490
e. Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
f. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
g. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

B/F/TAF FDC was noninferior in achieving HIV-1 RNA < 50 copies/mL at Week 48 when compared to ABC/DTG/3TC and DTG+FTC/TAF, respectively. Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Studies 1489 and 1490, the mean increase from baseline in CD4+ count at Week 48 was 207, 229, and 201 cells per mm^3 in the pooled B/F/TAF FDC, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively.

Bone Mineral Density:

In Study 1489, bone mineral density (BMD) change from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (N = 257 and 267 in the B/F/TAF FDC group and N = 270 and 274 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage changes in BMD were similar in the B/F/TAF FDC group compared to the ABC/DTG/3TC group for hip (−0.8% vs. −1.0%) and lumbar spine (−0.8% vs.−0.6%).

Virologically Suppressed Patients

In Study 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to B/F/TAF FDC were evaluated in a randomized, double-blind study of virologically-suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (N = 563). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 3 months prior to study entry. Patients were randomized in a 1:1 ratio to either switch to B/F/TAF FDC at baseline (N = 282), or stay on their baseline antiretroviral regimen (N = 281). Patients had a mean age of 45 years (range 20-71), 89% were male, 73% were White, and 22% were Black. 17% of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 723 cells/mm^3 (range 124-2444).

In Study 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (boosted by either COBI or RTV) to B/F/TAF FDC were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N = 577). Patients must have been stably suppressed on their baseline regimen for at least 6 months and INSTI naïve prior to study entry. Patients were randomized in a 1:1 ratio to either switch to B/F/TAF FDC (N = 290), or stay on their baseline antiretroviral regimen (N = 287). Patients had a mean age of 46 years (range 20-79), 83% were male, 66% were White, and 26% were Black. 19% of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells/mm^3 (range 62-2582). Patients were stratified by prior treatment regimen. At screening, 15% of patients were receiving ABC/3TC plus ATV or DRV (boosted by either COBI or RTV) and 85% of patients were receiving FTC/TDF plus ATV or DRV (boosted by either COBI or RTV).

Treatment outcomes of Studies 1844 and 1878 through Week 48 are presented in Table 1-2.

Table 1-2. Virologic Outcomes of Studies 1844 and 1878 at Week 48[a]

	Study 1844		Study 1878	
	B/F/TAF FDC (N = 282)	**ABC/DTG/3TC (N = 281)**	**B/F/TAF FDC (N = 290)**	**Baseline ATV- or DRV-based regimen (N = 287)**
HIV RNA < 50 copies/mL	94%	95%	92%	89%
Treatment Difference (95% CI)	-1.4% (-5.5% to 2.6%)		3.2% (-1.6% to 8.2%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[c]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

a. Week 48 window was between Day 295 and 378 (inclusive).
b. Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
c. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent loss to follow-up, etc.

In Study 1844, at Week 48, switching to B/F/TAF FDC was noninferior to remaining on ABC/DTG/3TC. The percentages of patients with HIV-1 RNA ≥ 50 copies/mL and who maintained HIV-1 RNA < 50 copies/mL were similar between the B/F/TAF FDC and ABC/DTG/3TC groups. The mean change from baseline in CD4+ count at Week 48 was −31 cells per mm^3 in patients who switched to B/F/TAF FDC and 4 cells per mm^3 in patients who stayed on ABC/DTG/3TC.

In Study 1878, at Week 48, switching to B/F/TAF FDC was noninferior to remaining on an ATV- or DRV-based regimen. The percentages of patients with HIV-1 RNA ≥ 50 copies/mL and who maintained HIV-1 RNA < 50 copies/mL were similar between the B/F/TAF FDC and ATV- or DRV-based regimen groups. The mean change from baseline in CD4+ count at Week 48 was 25 cells per mm^3 in patients who switched to B/F/TAF FDC and 0 cells per mm^3 in patients who stayed on their baseline regimen.

Bone Mineral Density:

In Study 1844, BMD change from baseline to Week 48 was assessed by DXA. In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (N = 229 and 233 in the B/F/TAF FDC group and N = 242 and 244 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage increases in BMD were similar in the B/F/TAF FDC group compared to the ABC/DTG/3TC group for hip (0.2% vs. 0.3%) and lumbar spine (0.7% vs.0.4%).

1.3. Rationale for This Study

Despite the racial composition of the US HIV epidemic, African Americans have less access to and engagement with clinical studies of new antiretroviral therapy. Most phase 3 studies of INSTIs have only enrolled between 10 and 25% of participants who identified as Black or African American {Lennox 2009}, {Walmsley 2013}, {Arribas 2017}. The most recently FDA approved INSTI, BIC, included ~30-36% of participants who identified as Black or African Americans, a level of engagement that under-represents African Americans compared to the demographics of the US HIV epidemic {Gallant 2017}, {Sax 2017}.

Despite progress, these studies have not overcome racial disparities in the distribution of access to medical research opportunities. The resulting subgroup analyses have limited precision, and comparisons between racial groups fail to adequately control for unmeasured social circumstances or structural systems of discrimination in America that may impact healthcare outcomes. As a result, there is a need for further study of B/F/TAF in African Americans infected with HIV-1.

Total pill burden, dosing frequency, and safety concerns are among the greatest obstacles to achieving adherence {Stone 2002}, {Chesney 2000}. Incomplete adherence to ARV regimens is a critical factor contributing to the development of viral resistance and treatment failure and thus is a primary barrier to successful long-term treatment. {Maggiolo 2001}, {Felizarta 2004}, {Arribas 2004}, {Willig 2008}.

Regimen simplification of an established therapy may reduce pill burden and potentially enhance long-term safety and tolerability. B/F/TAF combines potent and sustained efficacy, favorable tolerability, minimal long-term toxicity, and practical, convenient dosing. This study will evaluate switching to B/F/TAF in African American participants who are virologically suppressed on their current regimen. The goal of this study is to assess whether switching to a single tablet regimen of B/F/TAF from a regimen of two NRTIs plus a third agent will provide comparable virologic control along with improved safety and tolerability.

1.4. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective antiretroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis {Department of Health and Human Services (DHHS) 2018}. The risk of class effects is considered to be low. Potential benefits may include provision of a new

ARV therapy which may have fewer side effects than alternative therapies resulting in improved adherence and long-term virologic suppression. 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 in African American patients. In phase 3 studies of B/F/TAF, the subgroup of participants self-identified as Black or African American had similar outcomes for efficacy and safety compared with the study population as a whole.

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

1.5. Rationale for Dose Selection

B/F/TAF

The B/F/TAF FDC containing B (50 mg), F (200 mg), and TAF (25 mg), has been approved by the US-FDA for use once daily for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. B/F/TAF contains 25 mg of TAF, the approved and recommended dosage for the treatment of HBV infection with other ARVs for treatment of HIV/HBV coinfection {Gunthard 2016}, {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}, {Terrault 2016}, {European Association for the Study of the Liver 2017}, {European AIDS Clinical Society (EACS) 2016}, and {Sarin 2016}.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of 2 NRTIs and a third agent to a fixed dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing their baseline regimen in HIV-1 infected, virologically suppressed African American participants as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24

The secondary objectives of this study are:

- To evaluate the efficacy of switching to a FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48

- To evaluate the efficacy, safety, and tolerability of switching to FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent in HIV-1 infected, virologically suppressed African American participants through Week 48

3. STUDY DESIGN

3.1. Endpoints

The primary efficacy endpoint is:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as defined by the US FDA-defined snapshot algorithm

The secondary efficacy endpoints are:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm
- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Weeks 24 and 48.

3.2. Study Design

This protocol describes a randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of B/F/TAF versus continuing a regimen of 2 NRTIs and a third agent in HIV-1 infected African American participants who are virologically suppressed (HIV-1 RNA < 50 copies/mL) for ≥ 6 months.

3.3. Study Treatments

Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

Treatment Group 1 (n=320): FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, once daily (QD), without regard to food.

Treatment Group 2 (n=160): Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, QD, without regard to food at Week 24.

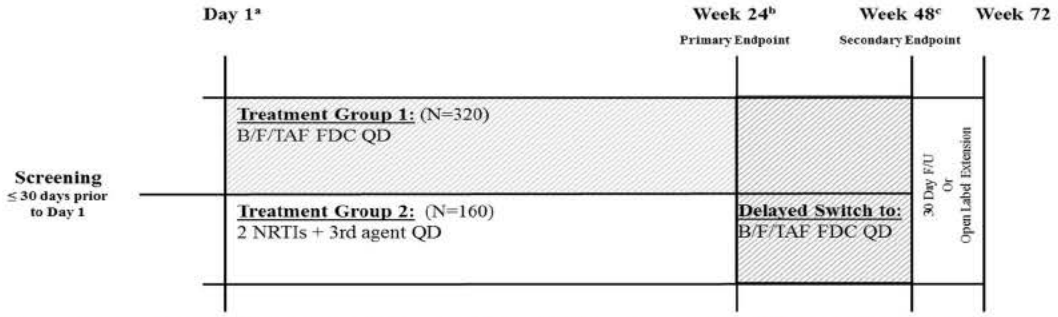
Randomization will be stratified as defined in Section 5.1.

3.4. Duration of Treatment and End of Study

Participants who meet eligibility criteria will be treated for at least 48 weeks. Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants randomized to SBR will have, after their delayed switch, an additional visit at Week 28.

Participants who complete the study through the Week 48 visit and wish to continue on B/F/TAF, will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and will attend study visits every 12 weeks followed by a 30-Day Follow-Up Visit. Participants who complete the study through the Week 48 Visit and do not continue their participation in the study, will be required to return to the clinic 30 days after their Week 48 Visit for a 30-Day Follow-Up Visit.

Figure 3-1. Study Schema



a Following the Day 1 visit, participants will be required to return for study visits at Weeks 4 and 12, and then every 12 weeks through the Week 48 visit. The Primary Endpoint will be assessed when the last enrolled participant completes the Week 24 visit.

b At Week 24, participants randomized to continue on their baseline regimen who complete 24 weeks of treatment on their baseline regimen will switch to FDC of B/F/TAF.

c At Week 48, participants who wish to continue on FDC of B/F/TAF will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and attend study visits every 12 weeks followed by a 30-Day Follow-up Visit.

3.5. Biomarker Testing

3.5.1. CCI [redacted]

[redacted]

3.5.2. CCI [redacted]

[redacted]

CCI [redacted]

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 480 participants who meet the eligibility criteria will be enrolled. Eligible participants with chronic hepatitis C virus (HCV) infection are permitted to enroll. In addition, eligible participants with chronic hepatitis B virus (HBV) infection are permitted to enroll if their baseline regimen contains either TAF or TDF.

4.2. Inclusion Criteria

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

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

2) Age ≥ 18 years

3) Self-describes as Black, African American, or mixed race including Black

4) Currently receiving an ARV regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed 3rd agent for ≥ 6 months

    a) Allowed 3rd agents include any FDA-approved INSTI, with the exception of bictegravir, any FDA-approved NNRTI with the exception of etravirine, and FDA-approved PI or the CCR5 antagonist, maraviroc

    b) If the baseline 3rd agent is dolutegravir, dosing other than 50 mg once daily is excluded

    c) Baseline regimens containing investigational drugs or > 2 classes of ARVs are not permitted, with the exception of the pharmacologic enhancers cobicistat (taken with elvitegravir or a PI), or ritonavir (taken with a PI)

5) Have no documented or suspected resistance to INSTIs and no history of virologic failure on an INSTI containing regimen (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving <50 copies/mL while on an INSTI-containing regimen)

6) History of 1-2 thymidine analogue mutations (TAMs; M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), M184V/I, and RT substitutions not described in exclusion criterion 1 are allowed. Any NNRTI or PI resistance mutations are allowed.

7) Documented plasma HIV-1 RNA < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months and at least the last two HIV-1 RNA measurements prior to the Screening visit

    a) Must include one or more HIV-1RNA tests within the 12 months prior to screening

8) Willingness to wait approximately 6 months before switching from current ARVs

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

10) Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault (C-G) formula {Cockcroft 1976}:

Male:

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

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

Female:

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

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

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

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

13) Total bilirubin ≤ 1.5 mg/dL (≤ 26 umol/L), **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))

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

16) Persons of childbearing potential (as defined in Appendix 6) must have a negative serum pregnancy test at screening and clinic admission.

17) Male participants and persons of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 6

18) Participants must agree to refrain from egg donation from first dose of FDC of B/F/TAF and throughout the study period as described in Appendix 6.

19) Life expectancy ≥ 1 year

4.3. Exclusion Criteria

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

1) History of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT will be excluded

2) No desire to switch from current ARVs

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

4) Participants experiencing decompensated cirrhosis (e.g., ascites, encephalopathy, or variceal bleeding)

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

6) 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.

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

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

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

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

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

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

13) Females who are breastfeeding

14) Participants receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with FDC of B/F/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.

15) Acute hepatitis in the 30 days prior to randomization

16) Active tuberculosis infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

Participants will be assigned a screening number in the Interactive Web Response System (IWRS) at the time of consent. **Randomization and Day 1 visits cannot occur until participant eligibility has been confirmed.**

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

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

Treatment Group 1 (n=320): FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, once daily (QD), without regard to food.

Treatment Group 2 (n=160): Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, QD, without regard to food at Week 24.

The IWRS will assign study drug bottle numbers of open label FDC of B/F/TAF at each study visit for participants in Treatment Group 1 and at each study visit starting at Week 24 for participants in Treatment Group 2.

Randomization will be stratified by the baseline 3rd agent ARV class at entry (integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or CCR5 antagonist).

5.2. Description and Handling of B/F/TAF

5.2.1. Formulation

5.2.1.1. B/F/TAF (50/200/25 mg)

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

5.2.2. Packaging and Labeling

5.2.2.1. B/F/TAF (50/200/25 mg)

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

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

5.2.3. Storage and Handling

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 participants, all bottles of B/F/TAF should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, B/F/TAF should not be stored in a container other than the container in which it was 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 through inhalation when handling.

5.3. Dosage and Administration of B/F/TAF

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

Treatment Group 1 (n=320): FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, once daily (QD), without regard to food.

Treatment Group 2 (n=160): Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, QD, without regard to food at Week 24.

After Week 48, all participants who wish to continue on B/F/TAF, will receive B/F/TAF once daily for up to an additional 24 weeks.

Participants will be instructed to bring all study medication in the original container to each clinic visit for drug accountability. The Investigator will be responsible for maintaining accurate records for all B/F/TAF 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

Treatment Group 1 (B/F/TAF) and Treatment Group 2 (SBR) After Switch to B/F/TAF at Week 24

The use of medications for the treatment of HIV, other than B/F/TAF, is prohibited.

Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while participants are participating in the study.

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	
Hypoglycemic agent		Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.
Herbal/Natural Supplements	St. John's Wort	

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

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

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

Treatment Group 2 (SBR) Prior to Week 24

Investigators should refer to the current product/package inserts of the antiretroviral medications for contraindications and dose recommendations with concomitant medications related to their use.

5.5. Accountability for B/F/TAF

The investigator is responsible for ensuring adequate accountability of all used and unused B/F/TAF. This includes acknowledgement of receipt of each shipment of B/F/TAF (quantity and condition). All used and unused B/F/TAF dispensed to participants 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 B/F/TAF kits
- Record the date, participant number, participant initials, the B/F/TAF kit number dispensed
- Record the date, quantity of used and unused B/F/TAF returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Return and disposal of B/F/TAF will be performed as outlined in Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant 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. Participant Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that participants are eligible for study prior to enrollment. Please refer to Section 6.3 for details about randomization and treatment assignment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent(s)
- Obtain demographic information, including gender at birth, sexual orientation, and gender identity
- Obtain screening number in IWRS
- Obtain medical history including history of HIV-1 disease-related events, and prior medications within 30 days of the screening visit
- If available, obtain documentation of historical genotype(s) **(not required for entry to study)**
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 12-lead ECG performed supine
- Height
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2
- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form

Participants meeting all of the inclusion criteria, and none of the exclusion criteria, will return to the clinic within 30 days after screening for the Day 1 Visit. Participants randomized to Treatment Group 1 must continue to take their prior treatment regimen up until the day before their scheduled Day 1 visit. Participants randomized to Treatment Group 2 will continue to take their prior treatment regimen until they switch to FDC of B/F/TAF at Week 24.

From the time of obtaining informed consent through the first administration of study treatment, record all SAEs, as well as any AEs related to protocol-mandated procedures on the adverse events 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.

6.3. Randomization

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

6.4. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. **The Investigator must have confirmed eligibility before proceeding with the Day 1 visit.** Participants in Treatment Group 1 must complete all study procedures before being administered FDC of B/F/TAF:

- HIV Symptoms Distress Module Index and HIV Treatment Satisfaction Status (HIV-TSQs) are to be completed by the participant. Visual Analogue Scale (VAS) Adherence Questionnaire is to be completed by participants in Treatment Group 2 only. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2.
- Dispense FDC of B/F/TAF for participants in Treatment Group 1

- Observed first dose administration of FDC of B/F/TAF in Treatment Group 1 as described in Section 5.3. If the participant has taken their prior regimen on Day 1, prior to the Study Visit, they should be instructed to take their first dose of B/F/TAF the following day and dosing can be confirmed by phone.

- Participants should be instructed to take FDC of B/F/TAF without regard to food. The participant should be counseled regarding the importance of adherence and taking their study medication at approximately the same time each day as directed by the Investigator.

6.5. Treatment Assessments (Week 4-48)

The following evaluations are to be completed at Weeks 4, 12, 24, 36, and 48 unless otherwise specified. Participants randomized to SBR will have, after their delayed switch, an additional visit at Week 28.

All study visits are to be completed within ± 6 days of the protocol specified visit date (based on the Day 1 visit), unless otherwise specified.

Regularly scheduled evaluations will be made on all participants whether or not they continue to receive their study treatment regimen.

- HIV Symptoms Distress Module Index is to be completed by the participant at **Weeks 4, 24, 28 (SBR only) and 48**. HIV Treatment Satisfaction Change (HIV-TSQc) is to be completed at **Weeks 4 and 24 only**. VAS Adherence Questionnaire is to be completed by the participant at **Weeks 4, 12, and 24** in Treatment Group 2 only. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires

- Review of AEs and changes in concomitant medications

- Complete physical examination **(Weeks 24 and 48)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination, as needed

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

- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2

- Document dispensation and accountability for FDC of B/F/TAF dispensed for Treatment Group 1 for all visits and starting at Week 24 for Treatment Group 2.

- Participants who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Section 6.13.1 and 6.13.2

6.6. Treatment Assessments (Post Week 48)

6.6.1. Post Week 48 Assessments

At the Week 48 visit, participants who wish to continue on FDC of B/F/TAF, will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and will attend study visits every 12 weeks followed by a 30-Day Follow-Up Visit. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.

- Review of AEs and changes in concomitant medications
- Complete physical examination **(Week 72)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2
- Document dispensation and accountability for FDC of B/F/TAF dispensed
- Participants who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Section 6.13.1 and 6.13.2

6.7. Post-Treatment Assessments

6.7.1. Early Study Drug Discontinuation Assessments

If the participant discontinues their study regimen prior to the Week 48 visit, the participant will be asked to return to the clinic within 72 hours of stopping study treatment for the Early Study Drug Discontinuation Visit. The participant will be asked to continue attending the scheduled study visits through the Week 48 visit. Participants on Treatment 2 (SBR) who discontinue their baseline regimen due to an AE prior to Week 24 will be asked to continue attending the scheduled study visits through the Week 24 visit.

At the Early Study Drug Discontinuation Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study treatment regimen, will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)

- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2
- Document study drug accountability for FDC of B/F/TAF dispensed

6.7.2. 30-Day Follow-up Visit

Participants who complete the study through the Week 48 Visit and do not continue their participation in the study, will be required to return to the clinic 30 days after their Week 48 Visit for a 30-Day Follow-Up Visit.

Participants who prematurely discontinue study treatment and refuse to continue in the study through the Week 48 visit will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-up Visit.

Those participants who prematurely discontinue study treatment 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, as long as the visit is > 30 days after last dose.

Participants who participate post Week 48 will complete a 30-Day Follow-up Visit 30 days after the last dose of B/F/TAF.

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

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.9.1 and 6.9.2

At the 30-Day Follow-Up Visit, any evaluations showing abnormal results believed to be a reasonable possibility of a causal relationship with study treatment will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

6.8. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Participant request to discontinue for any reason
- Pregnancy during the study; refer to Appendix 6

  Note: Female participants who become pregnant during the study will be discontinued from the study.
- Development of active tuberculosis infection
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB)

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 participant may resume study dosing at the discretion of the investigator.
- Lack of efficacy
- Participant noncompliance

6.9. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below, within Section 6, and in Appendix 2 Study Procedures Table.

6.9.1. Blood Samples

- Blood sample collection for the following laboratory analyses will be performed at every study visit, unless otherwise specified:
  - Serum pregnancy test (all female participants). If the test is positive, the participant will not be enrolled **(Screening only).**
  - FSH test: Required for female participants who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure **(Screening only)**

— Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, blood urea nitrogen (BUN), chloride, creatinine, glucose, potassium, sodium, amylase, and Cystatin C

- Calcium, phosphorus, magnesium, amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × ULN) **(Screening and Day 1 only)**
- Cystatin C **(Day 1 only)**

— Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) collected at **Day 1, Weeks 24, 48, and 72.**

- If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments

— eGFR according to the Cockcroft-Gault formula:

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

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

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

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.\ 6786} \times 0.85 = \text{CLcr (mL/sec)}$$

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

— CD4+ cell count and percentage (**Screening, Day 1, Weeks 24, 48, and 72, 30 Day Follow-up and ESDD**)

— Plasma HIV-1 RNA. Any subsequent HIV-1 genotype and phenotype testing will be performed as described in Sections 6.13.1 and 6.13.2.

— HBV blood panel (**Screening and Week 48**): 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:

- *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

— Plasma HBV DNA for patients who are HBV co-infected (**Day 1, Week 24, Week 48, and ESDD)**

HBV coinfection, for the purposes of this study, is defined as any one of the following two criteria on or prior to Day 1:

1. Positive HBsAg
2. Negative HBsAg, negative HBsAb, positive HBcAb and quantifiable HBV DNA (HBV DNA ≥20 IU/mL)

— HCV antibody (Ab) serology (**Screening, Week 48, and Week 72**). Participants who are HCVAb positive will have a HCV RNA test performed.

— Mandatory Whole blood for HIV-1 DNA archive testing (**Day 1 for all participants, and at Week 24 for participants randomized to SBR only)**

— CCI [redacted].

— Plasma and serum storage sample for safety, virology, or PK testing (Not collected at Screening and 30-day Follow-up Visits)

6.9.2. Urine Samples

Urine samples will be collected for the following laboratory analyses will be performed at every study visit, unless otherwise specified:

- Urinalysis
- Urine pregnancy testing (Not collected at Screening) for persons of childbearing potential. If result is positive, a serum pregnancy test will be performed.
- Urine storage sample (Not collected at Screening and 30-day Follow-up Visits)

6.9.3. Blood Storage Samples

A portion of the blood and urine samples drawn at all visits (except the Screening Visit, 30-day follow-up Visit and Unscheduled Visits) will be frozen and stored. These stored blood and urine samples may be used by the Sponsor or its research partners to help answer questions about B/F/TAF, about the disease and its associated conditions and/or to provide additional safety data. No human genetic testing will be performed without expressed consent of study participants. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences for a period up to 15 years.

6.10. Assessments for Premature Discontinuation from Study

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study, and continue to perform the required study-related follow-up and procedures (See Section 6.8, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.11. End of Study

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

6.12. Post Study Care

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

6.13. 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, Week 24, or Week 48.

6.13.1. Management of Virologic Rebound

Participants 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, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (within 2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA ≥ 50 copies/mL). Participants 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 participant's first post-Day 1 resistance test, additional testing will be conducted on a case-by-case basis. Any participant may be discontinued at Investigator's discretion or per local treatment guidelines.

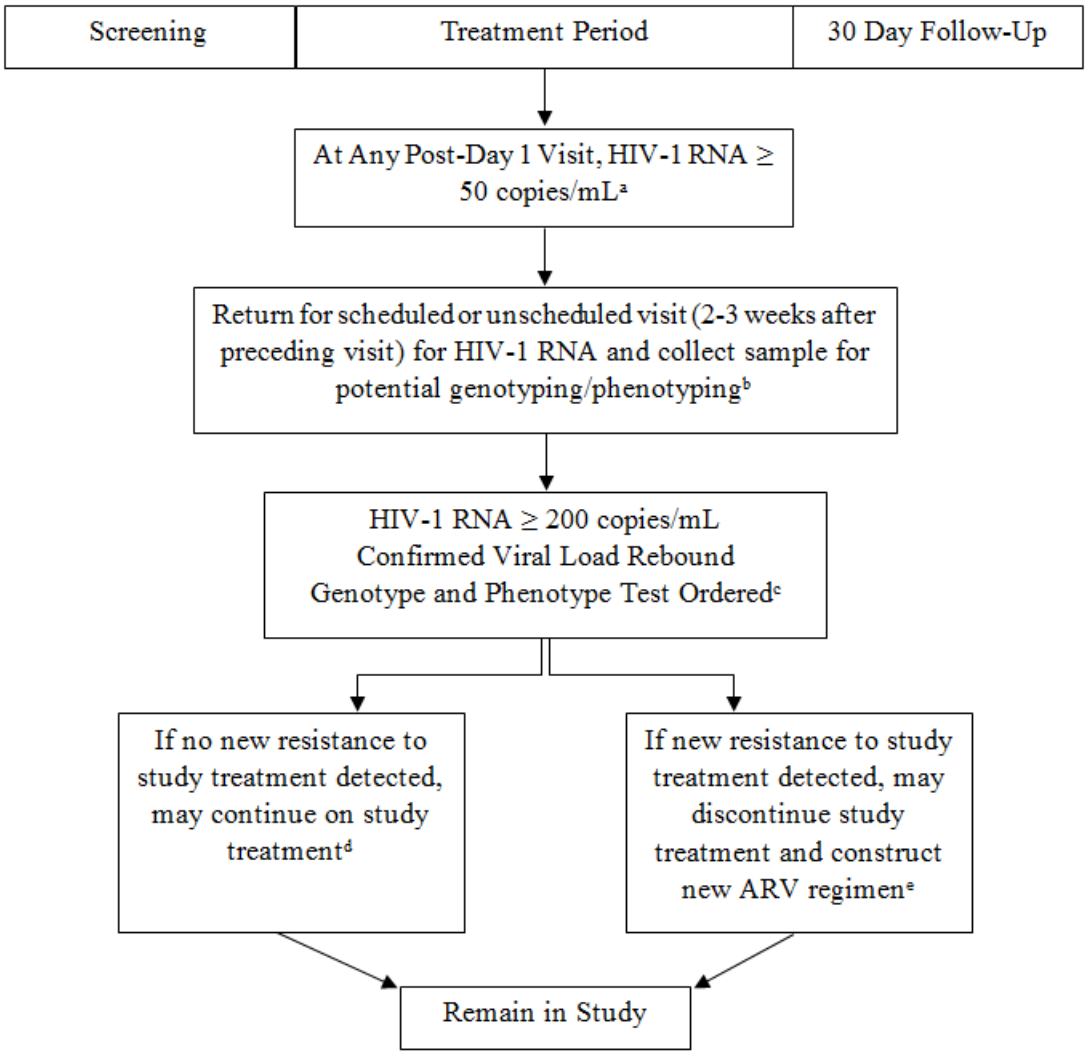
If no resistance to study treatment is detected from the genotype or phenotype, the participant may remain on study treatment and HIV-1 RNA should be analyzed at a new visit (within 2 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and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

Participants 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 treatment for an individual participant must discuss with the Medical Monitor prior to study drug discontinuation.

For participants who are off study treatment 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 participants 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 treatment continuation/discontinuation options and discuss with the Medical Monitor prior to study treatment discontinuation.
d. If no new resistance to study treatment is detected, HIV-1 RNA will be repeated 2 – 3 weeks later. Investigator reviews study treatment continuation/discontinuation options and discuss with the Medical Monitor prior to study treatment discontinuation. The participant will remain in the study.
e. A new ARV regimen may be configured, at the Investigator's discretion and the participant will remain in the study.

6.13.2. Participants with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation, Week 24, or Week 48

Participants with HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation, last visit, or last Week 24 or Week 48 result will be considered virologic failures. Participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 or Week 48 will be asked to return for an unscheduled visit within the visit window for a retest.

Participants with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit, or Week 24 or Week 48 visit, 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 participant administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history 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 participant 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 participant 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 participant to expedited reporting requirements.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

- **No: Evidence** exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the 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.

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

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

Requirements for collection prior to study treatment initiation:

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

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

7.3.1. Adverse Events

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

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant 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 PVE 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 PVE.

Electronic Serious Adverse Event Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE 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 PVE contact information: Email: PPD
  Fax: 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.

- 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 participant's eCRF and the event description section of the SAE form

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax only when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to

worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

7.5. Clinical Laboratory Abnormalities

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

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

7.6. Toxicity Management

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

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

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

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

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

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

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

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

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

For participants defined as having HBV infection, an On-Treatment ALT Flare is classified 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.

7.6.4.1. Management of ALT Flare in Participants Receiving Study Medication

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

- Schedule the participant 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 participant will be performed. The assessment should include a physical examination and evaluation of the participant's mental status.
- If the ALT elevation is confirmed, request the central clinical laboratory to conduct reflex testing for PT/INR, plasma HBV DNA, HBV serology (HBsAg, HbsAb, HbeAg and HbeAb), HDV, HAV IgM, and HCV serology
- Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and serum albumin. Based on the results of the confirmatory tests, the following treatment modifications are recommended.

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

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

Elevated Liver Enzymes, Elevated Liver Function Tests

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

7.6.4.2. Management of Exacerbation of Hepatitis B in Participants 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 participant is on no post-study therapy for HBV, the following is recommended:

- Schedule the participant 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 participant.
- 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,HbsAb, HbeAg, HbeAb), HDV, HAV IgM and HCV. If plasma HBV DNA is increasing, the investigator should consider immediate initiation of approved therapy.
- The participant 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.

7.6.5. Management of Potential Nephrotoxicity

Estimated glomerular filtration rate (eGFR), according to the Cockcroft-Gault formula for creatinine clearance, will be followed post-baseline during the study. All participants with estimated eGFR < 50 mL/min must have serum creatinine measured again within 3 calendar days of receipt of results.

At the time of this repeat serum creatinine assessment, Cystatin C will also be measured and the eGFR by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement.

Any participants who have an eGFR < 50 mL/min that also experience > 20% reduction in eGFR by CKD-EPI (cystatin C) from baseline or who have other clinical and/or laboratory evidence of acute renal failure will be discussed with the Medical Monitor and potentially discontinue from study drug.

For participants with eGFR < 50 mL/min who are not discontinued based on toxicity management procedures above and considered to have stable renal function per Principal Investigator and Medical Monitor, it is not mandatory to repeat eGFR assessments within 3 days. Participants in Treatment Group 2 (SBR) should have dose adjustments made to their ARVs as clinically appropriate.

CKD-EPI (cystatin C) formula adjusted for age and sex:

eGFR (mL/min/1.73m^2) = 133 x min(Scys/0.8,1)$^{-0.499}$ × max(Scys/0.8,1)$^{-1.328}$ × 0.996^{Age} [× 0.932 if female]

Where Scys is serum cystatin C (mg/L), min (Scys/0.8,1) indicates the minimum of Scys/0.8 or 1, and max (Scys/0.8,1) indicates the maximum of Scys/0.8 or 1.

Once an individual participant has developed any of these renal changes and followed the management guidelines above, it is not necessary to have repeat evaluations if it is determined that it is safe for that participant to continue on treatment with standard follow-up visits as described in the protocol

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

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

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

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 participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the participant 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.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

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

Any complications during pregnancy and the outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:

Email: PPD and Fax: PPD

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

7.7.2.2. Reporting Other Special Situations

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

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of 2 NRTIs and a third agent to fixed dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing their baseline regimen in HIV-infected, virologically suppressed African American participants as determined by the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 24

The secondary objectives of this study are:

- To evaluate the efficacy of switching to FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent as determined by the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48

- To evaluate the efficacy, safety, and tolerability of switching to FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent in HIV-infected, virologically suppressed African American participants through Week 48

8.1.2. Primary Endpoint

The primary efficacy endpoint is:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as defined by the US FDA-defined snapshot algorithm

8.1.3. Secondary Endpoint

The secondary efficacy endpoints are:

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

- The proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and 48 as defined by the US FDA-defined snapshot algorithm

- The change from baseline in CD4+ cell count at Weeks 24 and 48.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

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

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set

The primary analysis set for efficacy analyses is defined as the full analysis set (FAS), which will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of study treatment, (3) have at least 1 post baseline HIV-1 RNA result while on study treatment, and (4) do not have pre-existing resistance-associated mutations. Participants will be grouped according to the treatment to which they were randomized.

8.2.1.2.2. Per-Protocol (PP) Analysis Set for anti-HIV Efficacy Analysis

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

Participants meeting any of the following criteria will be excluded from the Week 24 PP analysis set for anti-HIV efficacy analysis:

- Participants who do not have on-treatment HIV-1 RNA in the Week 24 analysis window, except when missing due to discontinuation of study treatment for lack of efficacy.
- Participants who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 4.3 including drugs not to be used with bictegravir.
- Nonadherence to study treatment: participants with adherence rate for active study treatment up to the Week 24 Visit below the 2.5th percentile
- Participants who do not meet the inclusion criteria for history of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT, including pre-existing mutations that are detected post-baseline

8.2.1.3. Safety

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

8.3. Data Handling Conventions

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

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

Demographic data will include sex, race, ethnicity, age, sexual orientation and gender identity.

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

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

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary analysis will consist of a non-inferiority test of switching to FDC of B/F/TAF versus SBR, with respect to the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24, as defined by the US FDA-defined snapshot algorithm. The primary analysis of the efficacy endpoint will be based on the FAS.

8.5.1.1. US FDA-defined Snapshot Algorithm

All HIV-1 RNA data collected on-treatment (ie, including data collected up to 1 day after the last dose date of study drug) will be used in the snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL**: this includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 24 analysis window
- **HIV-1 RNA ≥ 50 copies/mL**: this includes participants
  a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window, or
  b) Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and
     1. Who discontinue study treatment prior to or in the Week 24 analysis window due to lack of efficacy, or
     2. Who discontinue study treatment prior to or in the Week 24 analysis window due to reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- **No Virologic Data in the Week 24 Analysis Window**: this includes participants who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:
  a) Discontinuation of study treatment prior to or in the Week 24 analysis window due to reasons other than lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  b) Missing data during the window but on study treatment

8.5.1.2. Analysis of Primary Efficacy Endpoint

The null hypothesis is that the proportion of participants achieving HIV-1 RNA < 50 copies/mL (as defined by the US FDA-defined snapshot algorithm) at Week 24 in B/F/TAF is at least 6% lower than the response rate in SBR; the alternative hypothesis is that the response rate in B/F/TAF is less than 6% lower than that in SBR.

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

It will be concluded that FDC of B/F/TAF is non-inferior to SBR if the upper bound of the 2-sided 95% CI of the difference between treatment groups [B/F/TAF – SBR] in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL is less than 6% (i.e., a margin of 6% is applied to non-inferiority assessment).

If non-inferiority of B/F/TAF to SBR is established, the upper bound of the 95% CI will be compared to 0; if the upper bound of the 95% CI is less than 0, superiority of B/F/TAF over SBR will be established.

8.5.2. Secondary Analyses

The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48, and the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be summarized.

The changes from baseline in CD4+ cell count at Weeks 24 and 48 will be summarized by treatment using descriptive statistics. The differences between treatment groups at Week 24 and the associated 95% CIs will be constructed using an Analysis of Variance (ANOVA) model, including treatment (B/F/TAF vs. SBR) as a fixed effect in the model.

8.6. Safety Analysis

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

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

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

8.6.1. Extent of Exposure

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

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

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

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

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

8.6.3. Laboratory Evaluations

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

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

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

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

8.6.4. Other Safety Evaluations

Vital signs will be summarized as appropriate.

8.7. Patient Reported Outcomes (PRO)

The PRO measures based on questionnaires will be summarized by treatment and visit using descriptive statistics.

8.8. Sample Size

Sample sizes of 320 in B/F/TAF FDC and 160 in SBR Group achieve approximately 89% power to detect a non-inferiority margin difference between the group proportions of 0.06 for HIV-1 RNA ≥ 50 copies/mL at Week 24. The assumed reference group proportion is 0.04. The treatment group proportion is assumed to be 0.10 under the hypothesis of inferiority. The power is computed for the case when the actual treatment group difference is zero (treatment = reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025.

8.9. Analysis Schedule

The Week 24 and 48 analyses will be conducted after all participants either complete their Week 24 and 48 visits or prematurely discontinue from the study treatment, respectively. Final analysis will be performed after all participants complete the study or prematurely discontinue from the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. 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 participant completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)

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 participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study participant activities until approval from the IRB 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 any modifications made to the protocol or any accompanying material to be provided to the participant after initial approval, with the exception of those necessary to reduce immediate risk to study participants.

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-approved consent form for documenting written

informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or local requirements. The consent form will inform participants about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only participant 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 participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial. Participant 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) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB 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 participant:

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

- Documentation of the reason(s) a consented participant 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 participant, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each participant 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 (eg, 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 study drug 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 study drug disposal procedures and provide appropriate instruction for destruction of unused study drug 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 study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs, or 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 participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant 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 and IRBs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the participants' 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.

Arribas JR, Iribarren JA, Knobel H, Ribera E, Rubio R, Viciana P. Adherence, treatment satisfaction and effectiveness of once-daily (QD) vs twice-daily (BID) antiretroviral therapy (AT), in a large prospective observational cohort (CUVA Study). [Poster WePeB5780]. . XV International AIDS Conference; 2004 July 11-16; Bangkok, Thailand.

Arribas JR, Thompson M, Sax PE, Haas B, McDonald C, Wohl DA, et al. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. J Acquir Immune Defic Syndr 2017;75 (2):211-8.

Bailey ZD, Krieger N, Agenor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. Lancet 2017;389:1453-63.

Centers for Disease Control and Prevention (CDC). HIV and African Americans: HIV Diagnoses In 2016. Fact Sheet. 2018:

Chesney M. Factors affecting adherence to antiretroviral therapy. Clin Infect Dis. 2000;30 (Suppl 2):S-171-S6.

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.

Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2018:298.

European AIDS Clinical Society (EACS). Guidelines Version 8.1 English. October, 2016.

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol 2017;67 (2):370-98.

Felizarta F, Becker S, Bellos N, Jayaweera D, Sands M, Slater L. Adherence and efficacy with a once-daily efavirenz-based regimen: 48-week results from the Daily Antiretroviral Therapy II (DART II) Study [Poster 5842]. . XV International AIDS Conference; 2004 July 11-16; Bangkok, Thailand.

Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, Emtricitabine, and Tenofovir Alafenamide Versus Dolutegravir, Abacavir, and Lamivudine for Initial Treatment of HIV-1 Infection (GS-US-380-1489): A Double-Blind, Multicentre, Phase 3, Randomised Controlled Non-Inferiority Trial. Lancet 2017;390:2063-72.

Grabowski MK, Serwadda DM, Gray RH, Nakigozi G, Kigozi G, Kagaayi J, et al. HIV Prevention Efforts and Incidence of HIV in Uganda. N Engl J Med 2017;377 (22):2154-66.

Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016;316 (2):191-210.

Jensen-Fangel S, Pedersen L, Pedersen C, Larsen CS, Tauris P, Moller A, et al. The effect of race/ethnicity on the outcome of highly active antiretroviral therapy for human immunodeficiency virus type 1-infected patients. Clin Infect Dis 2002;35 (12):1541-8.

Joint United Nations Programme on HIV/AIDS (UNAIDS). Global Aids Update 2016. Available at: http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016. 31 May. 2016.

King WD, Minor P, Ramirez Kitchen C, Ore LE, Shoptaw S, Victorianne GD, et al. Racial, gender and geographic disparities of antiretroviral treatment among US Medicaid enrolees in 1998 [Author Manuscript]. J Epidemiol Community Health 2008;62 (9):798-803.

Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities [Author Manuscript]. Current HIV/AIDS reports 2011;8 (1):62-72.

Lemly DC, Shepherd BE, Hulgan T, Rebeiro P, Stinnette S, Blackwell RB, et al. Race and sex differences in antiretroviral therapy use and mortality among HIV-infected persons in care. J Infect Dis 2009;199 (7):991-8.

Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009;374 (9692):796-806.

Maggiolo F, Migliorino M, Maserati R, Rizzi L, Pan A, Rizzi A. Once-a-day treatment for HIV infection: Final 48-week results. [Abstract 320]. 8th Conference on Retroviruses and Opportunistic Infections; 2001 February 4-8; Chicago, IL.

Meditz AL, MaWhinney S, Allshouse A, Feser W, Markowitz M, Little S, et al. Sex, race, and geographic region influence clinical outcomes following primary HIV-1 infection. J Infect Dis 2011;203 (4):442-51.

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.

Oramasionwu CU, Brown CM, Lawson KA, Ryan L, Skinner J, Frei CR. Differences in national antiretroviral prescribing patterns between black and white patients with HIV/AIDS, 1996-2006 [Author Manuscript]. South Med J 2011;104 (12):794-800.

Oramasionwu CU, Koeller JM, Lawson KA, Brown CM, Morse GD, Frei CR. The state of disparities in opportunistic infection prophylaxis for blacks with HIV/AIDS. [Author Manuscript]. Medical care 2012;50 (11):920-7.

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.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated : 27 March. 2018.

Ribaudo HJ, Smith KY, Robbins GK, Flexner C, Haubrich R, Chen Y, et al. Racial differences in response to antiretroviral therapy for HIV infection: an AIDS clinical trials group (ACTG) study analysis. Clin Infect Dis 2013;57 (11):1607-17.

Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10 (1):1-98.

Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide Versus Dolutegravir With Emtricitabine and Tenofovir Alafenamide, For Initial Treatment of HIV-1 Infection (GS-US-380-1490): A Randomised, Double-Blind, Multicentre, Phase 3, Non-Inferiority Trial. Lancet 2017;390:2073-82.

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.

Stone VE, Jordan J, Tolson J, Pilon T. Potential impact of once daily regimens on adherence to HAART [abstract]. . 40th Annual Meeting of the Infectious Disease Society of America; 2002 Oct 24-27; Chicago. pp. p.129, Abstract 486.

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63 (1):261-83.

Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013;369 (19):1807-18.

Willig JH, Abroms S, Westfall AO, Routman J, Adusumilli S, Varshney M, et al. Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. AIDS 2008;22 (15):1951-60.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching From a Regimen of Two Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI) plus a Third Agent to a Fixed Dose Combination (FDC) of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF), in Virologically-Suppressed, HIV-1 Infected African American Participants

GS-US-380-4580 Original Protocol, 27 June 2018

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

PPD

Author

27 JUNE 2018

Date

PPD

Signature

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
Informed Consent	X										
HIV Symptoms Distress Module		X	X		X	X		X			
HIV-TSQ[h]		X	X		X						
VAS Adherence Questionnaire[i]		X	X	X	X						
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete/Symptom-Directed Physical Exam[j]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X										
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[l]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[l]	X										
FSH Test[m]	X										
Chemistry Profile[n]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[o]		X			X			X	X		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[p]	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[q]	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and Percentage[r]	X	X			X			X	X	X	X

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
HBV Blood Panel[s]	X[t]							X[t]			
Plasma HBV DNA[u]		X			X			X			X
HCV Serology[v]	X							X	X		
HIV-1 Genotype/Phenotype[q]											X[q]
Plasma, Serum, and Urine Sample Storage[w]		X	X	X	X	X	X	X	X		X
Whole Blood for HIV-1 DNA archive testing		X			X[x]						
CCI											
Obtain Screening Number	X										
Randomization[z]		X									
Study Drug Dispensation		X[bb]	X[bb]	X[bb]	X[aa]	X	X	X	X		
Study Drug Accountability			X[bb]	X[bb]	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Participants should initiate dosing of study drug on the same day as the Day 1 visit.
c All study visits are to be completed ± 6 days of the protocol-specified visit date (based on the Day 1 visit), unless otherwise specified.
d Participants randomized to continue their baseline regimen will have an additional visit at Week 28.
e At the study Week 48 Visit, participants who wish to continue on B/F/TAF will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and attend study visits every 12 weeks (± 6 days of the protocol specified visit date) followed by a 30 Day Follow-Up Visit.
f Must be completed 30 days after discontinuing study drug. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. Required for participants who permanently discontinue study drug prior to Week 48 and do not continue in the study through at least one subsequent visit after the ESDD visit. Participants who participate post Week 48 will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit.
g Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Participants will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the participant discontinues study drug. Participants on Treatment 2 (SBR) who discontinue their baseline regimen due to an AE prior to Week 24 will be asked to continue attending the scheduled study visits through the Week 24 visit.
h HIV-TSQs is to be completed at Day 1. The HIV-TSQc is to be completed at Week 4 and Week 24. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
i VAS Adherence Questionnaire will be administered at Day 1 and at all visits up to (and including) Week 24 for participants in Treatment Group 2 (SBR) only.
j Complete physical exam is required at Screening, Day 1, Week 24, 48, 72, and ESDD. Urogenital/anorectal exams will be performed at the discretion of the Investigator. Symptom-directed physical examination, as needed.
k. Vital signs measurements including blood pressure, pulse, respiratory rate, and temperature.
l All female participants will have a serum test performed at Screening. Urine pregnancy test will only be done for persons of childbearing potential. Positive urine pregnancy tests will be confirmed with a serum test.

m FSH test is required for female participants who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

n Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, amylase, and Cystatin C. After Day 1, calcium, phosphorous, magnesium, and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 x ULN) will not be collected. Analyses of glucose will be done as part of the fasting metabolic assessments, and not as part of the chemistry profile at Day 1, Weeks 24, 48, and 72. Cystatin C will only be collected at Day 1.

o Metabolic Assessments will be performed at Day 1, Weeks 24, 48, and 72. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

p CBC with differential and platelet count.

q HIV-1 genotype and phenotype testing for participants with confirmed virologic failure and HIV-1 RNA >200 copies/mL. Following virologic rebound, participants will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV-1 RNA and HIV-1 resistance analysis (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema.

r CD4+ Cell Count and Percentage to be collected at Screening and Day 1, and every 24 weeks thereafter, at Weeks 24, 48, and 72, in addition to the 30 Day Follow-up Visit and ESDD.

s HBV blood panel will be performed at Screening and Week 48: HBsAg, HBsAb, HBcAb.

t **For participants who are HBV co-infected (defined in Section 6.9.1):** The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative), and HBeAg (if negative, reflex HBeAb).
For participants who are NOT HBV co-infected: The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBcAb, and HBsAg. Participants who are HBsAg or HBcAb positive will have a reflex test for HBV DNA (viral load).

u **For participants who are HBV co-infected:** Plasma HBV DNA will be collected at Day 1, Week 24, Week 48 and ESDD.

v Hepatitis C virus serology will be performed at Screening, Week 48, and Week 72. Participants who are HCVAb positive will have a HCV RNA test performed.

w Plasma, serum ,and urine storage samples will be collected for safety, virology, or PK testing.

x Collect whole blood sample for participants randomized to SBR only at Week 24.

y CCI [redacted]

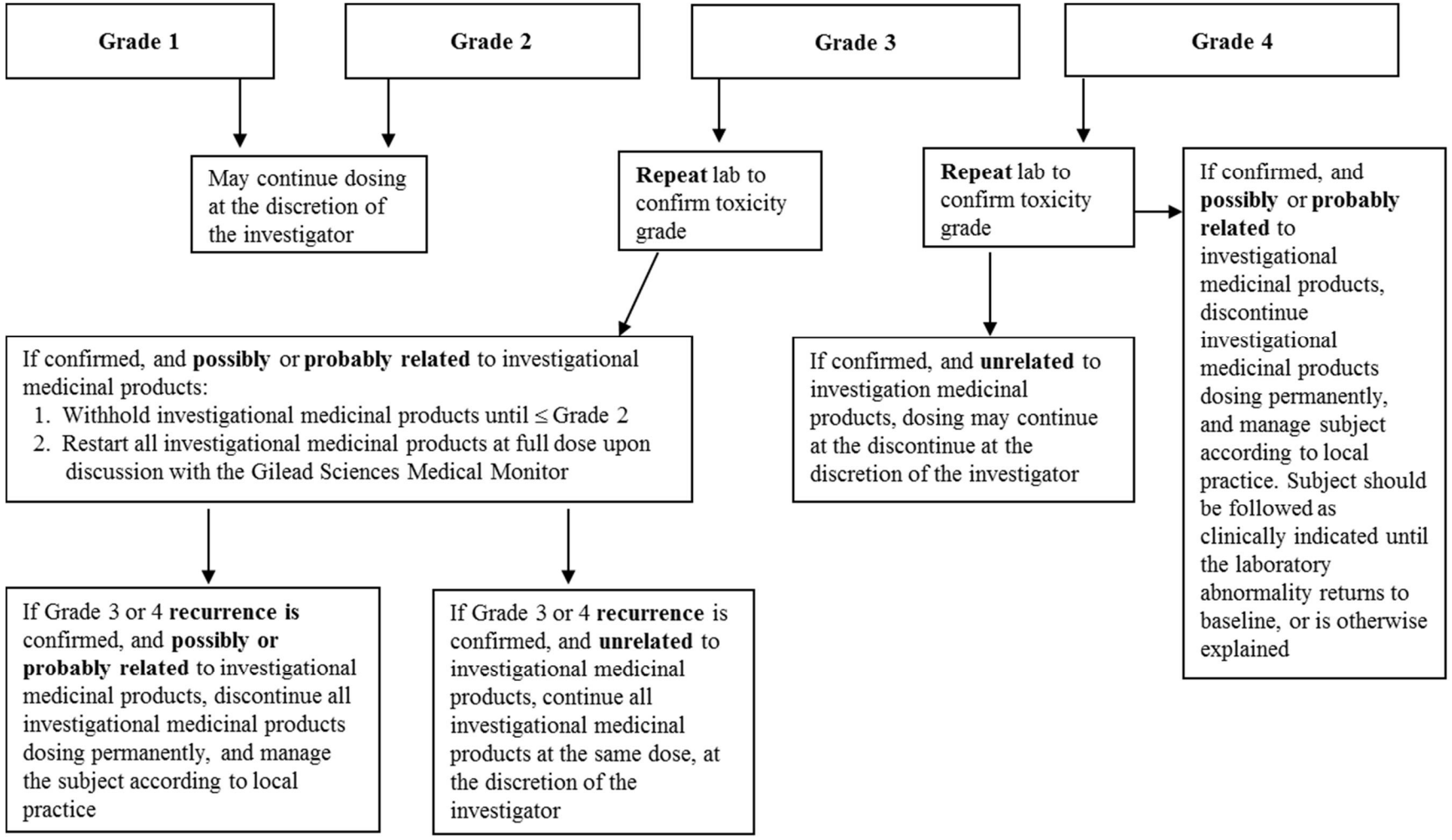
z Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.

aa At Week 24, participants randomized to continue their baseline regimen and complete 24 weeks of treatment on their baseline regimen will switch to FDC of B/F/TAF.

bb FDC of B/F/TAF will be dispensed to Treatment Group 1 only. Study drug accountability will be performed accordingly.

cc Subjects will receive study drug for dosing until Week 72.

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 **Adult and Pediatric,** **≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

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

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male participants >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 (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Central nervous system Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

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

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

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

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

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

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

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

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

Appendix 5. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

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

23) *Salmonella* septicemia, recurrent

24) Toxoplasmosis of brain

25) Wasting syndrome attributed to HIV infection

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

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

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range, and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Persons of Childbearing Potential

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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

Some anti-retroviral agents allowed under this protocol in the SBR arm are contraindicated in pregnancy as a malformation effect has been demonstrated/suspected or is unknown, taking into consideration class effects, or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy is based on non-clinical data. Some ARVs allowed in the SBR arm in this protocol have demonstrated/suspected or have insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Please refer to the latest prescribing information for comparator ARVs allowed under this protocol for additional information and for product-specific contraceptive recommendations.

Serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir. Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Please refer to the latest local product labeling for DTG for additional information.

b. Contraception Requirements for Persons of Childbearing Potential

The inclusion of persons of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed 7 days after the last study drug dose. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for persons of childbearing potential with infrequent or irregular periods. Female participants must also agree to one of the following from Screening until 30 days after the last dose of study drug.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success by hysterosalpingogram three months after procedure and where permitted and used per local prescribing label)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Persons of childbearing potential who wish to use a hormonally-based contraceptive method must use it in conjunction with a barrier method, preferably a male condom. Persons of childbearing potential who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide
- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

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

3) Contraception Requirements for Male Participants

During the study, male participants with persons of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Contraceptive Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the investigator if they become pregnant, or are concerned they may be pregnant, at any time during the study, or if they become pregnant within 30 days of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately.

Participants who become pregnant while on study should receive appropriate monitoring and care until the conclusion of the pregnancy. Subjects who become pregnant while on study who are not engaged in pre-natal care that includes a routine second trimester ultrasound will be referred for ultrasonography as part of study follow-up. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.7.2.1.