CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Fixed Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment Naïve, HIV-1 and Hepatitis B Co-Infected Adults	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	125,589	
EudraCT Number:	2018-000926-79	
Clinical Trials.gov Identifier:	NCT03547908	
Indication:	HIV-1/HBV Co-Infection	
Protocol ID:	GS-US-380-4458	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2:	02 March 2018 10 April 2018 06 July 2018

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Fixed Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment Naïve, HIV-1 and Hepatitis B Co-Infected Adults
IND Number:	125,589
EudraCT Number:	2018-000926-79
Clinical Trials.gov Identifier:	NCT03547908
Study Centers Planned:	Approximately 70 centers worldwide
Objectives:	The primary objective of this study is: • To evaluate the efficacy of fixed dose combination (FDC) of bictegravir /emtricitabine /tenofovir alafenamide (B/F/TAF) versus a regimen of dolutegravir (DTG) + emtricitabine/tenofovir disoproxil fumarate (F/TDF) in HIV and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48 • To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF in HIV and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 The secondary objectives of this study are: • To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 96 • To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96

	• To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with ALT normalization at Weeks 48 and 96 • To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with HBsAg loss at Weeks 48 and 96 • To evaluate the safety and tolerability of the two treatment groups through Week 96
Study Design:	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of a FDC of B/F/TAF versus DTG + F/TDF in HIV and HBV treatment-naïve, HIV-1 and HBV co-infected adult subjects. Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment groups: **Treatment Group 1 (n=120):** FDC of bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + placebo to match dolutegravir 50 mg and placebo to match FDC of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (F/TDF) administered orally, once daily, without regard to food **Treatment Group 2 (n=120):** dolutegravir 50 mg (DTG) + FDC of emtricitabine 200 mg/TDF 300 mg (F/TDF) + placebo to match FDC of B/F/TAF administered orally, once daily, without regard to food Randomization will be stratified by HBeAg (positive vs. negative), HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL), CD4+ cell count (< 50 cells/μL vs. ≥ 50 cells/μL) at Screening
Number of Subjects Planned:	Approximately 240 subjects
Target Population:	Antiviral HIV-1 and HBV treatment-naïve, HIV-1 and HBV co-infected adults
Duration of Treatment:	After screening, eligible subjects will be treated for at least 96 weeks during the blinded treatment phase. Following the Screening and Day 1 visits, subjects will be required to return for study visits at Weeks 4, 8, 12 and every 12 weeks thereafter. Once all subjects complete their Week 96 visit and Gilead completes the Week 96 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected subjects following

	review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open label (OL) extension phase or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. All subjects participating in the OL extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter. Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label extension phase, will be required to return to the clinic 30 days after the End of Blinded Treatment Visit for a 30-Day Follow-Up Visit. Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.
Diagnosis and Main Eligibility Criteria:	Subjects must meet ***all*** of the following inclusion criteria to be eligible to participate in the study. • HIV-1 co-infection: 1) Must be HIV antiretroviral treatment naive with plasma HIV-1 RNA ≥ 500 copies/mL at Screening 2) ≤ 10 days of prior therapy with any antiretroviral agent, including lamivudine, entecavir and approved or experimental integrase inhibitors following a diagnosis of HIV-1 infection (except the use for PrEP or PEP, up to one month prior to screening) 3) Screening HIV-1 genotype report must show sensitivity to FTC (emtricitabine) and TFV (tenofovir). • HBV co-infection: 4) Must be HBV treatment naïve (defined as < 12 weeks of oral antiviral treatment) 5) Screening HBV DNA ≥ 2,000 IU/mL • Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault (C-G) formula at the screening visit
Study Procedures/ Frequency:	After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 96 weeks. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks from Week 12

	though Week 96. After Week 96, all subjects will continue to take their blinded study drugs and attend study visit every 12 weeks until the End of Blinded Treatment Visit. Laboratory analyses (serum chemistry, liver function tests, hematology, urinalysis, pregnancy testing [for females of childbearing potential]), will be performed at the Screening, Day 1, and all subsequent study visits. HIV-1 RNA and CD4 + cell count will be performed at Screening, Day 1, and all subsequent study visits. HIV-1 genotype (RT and PR) will be determined at screening. Plasma HBV DNA levels, HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab) will be performed at Screening, Day 1, and every 12 weeks thereafter. Plasma HBV DNA will be monitored at all study visits. Serum samples for potential sequence analysis of HBV polymerase/reverse transcriptase (pol/RT) should be collected at all time points except screening. Sequencing analysis of the HBV pol/RT will be attempted for all viremic subjects (HBV DNA > 69 IU/mL) at Weeks 48, 96 or early study drug discontinuation as early as Week 8, as well as all subjects who meet virologic breakthrough criteria. Trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4, 12, and 36. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose at Weeks 8 and 24. Adverse events and concomitant medications will be assessed at each visit.
Test Product, Dose, and Mode of Administration:	FDC of bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg administered orally, once daily, without regard to food
Reference Therapy, Dose, and Mode of Administration:	dolutegravir 50mg + FDC of emtricitabine 200mg /tenofovir disoproxil fumarate 300mg administered orally, once daily, without regard to food
Criteria for Evaluation:	
Safety:	Adverse events and clinical laboratory tests to evaluate the safety and tolerability of the treatment regimens.

Efficacy:

The primary efficacy endpoints are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm
- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 by Missing = Failure approach

The secondary anti-HIV efficacy endpoints are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96.
- The change from baseline in CD4 cell count and CD4% at Weeks 48 and 96

The secondary anti-HBV efficacy endpoints are:

- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96
- The proportion of subjects with ALT normalization at Weeks 48 and 96
- The proportion of subjects with HBsAg loss at Weeks 48 and 96

Pharmacokinetics:

Trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4, 12, and 36. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose at Weeks 8 and 24.

The plasma concentrations of bictegravir, tenofovir alafenamide, and/or metabolites may be summarized using descriptive statistics.

CCI [redacted]

Statistical Methods:

The primary efficacy analysis will consist of a non-inferiority test of FDC of B/F/TAF versus DTG + F/TDF, with respect to the proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm. It will be concluded that B/F/TAF is non-inferior to DTG + F/TDF if the lower bound of the 2-sided 95% confidence interval (CI) of the difference (B/F/TAF – DTG + F/TDF) in the response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA-defined snapshot algorithm) is greater than -12%; ie, a margin of 12% is applied to non-inferiority assessment. The 95% CI will be constructed using a normal approximation method based on stratified Mantel-Haenszel proportions, where stratification factor includes baseline HIV-1 RNA (≤ 100,000 copies/mL vs. > 100,000 copies/mL).

The co-primary efficacy analysis will consist of a non-inferiority test of FDC of B/F/TAF versus DTG + F/TDF, with respect to the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 by Missing = Failure approach. It will be analyzed in a similar manner as described for the primary efficacy endpoint, except that the stratification factors include HBeAg status (positive vs. negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 og_{10} IU/mL).

To control type I error for the assessment of the primary and the co-primary efficacy endpoints, the hypothesis testing will be performed using the fallback procedure {Wiens 2005} in the sequential order with pre-specified 1-sided alpha level. The primary hypothesis of noninferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the FDA snapshot analysis) will be tested first. Non-inferiority test will be performed at one-sided, 0.025 alpha level. If non-inferiority is established, the co-primary hypothesis of noninferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 using Missing = Failure approach will be tested second at one-sided, 0.025 alpha level. Otherwise, the co-primary endpoint will not be tested at all.

The secondary anti-HIV efficacy endpoints include:

1) the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as defined by the US FDA-defined snapshot algorithm, which will be analyzed in a similar manner as described for the primary efficacy endpoint.

2) the change from baseline in CD4 and CD4% at Weeks 48 and 96, which will be summarized by treatment using descriptive statistics. The differences and the associated 2-sided 95% CIs will be constructed using an Analysis of Variance (ANOVA) model, including treatment (B/F/TAF vs. DTG + F/TDF), HIV-1 RNA (≤ 100,000 copies/mL vs. > 100,000 copies/mL) as fixed effects in the model.

The secondary anti-HBV efficacy endpoints include:

1) the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96
2) the proportion of subjects with ALT normalization at Weeks 48 and 96
3) the proportion of subjects with HBsAg loss at Weeks 48 and 96.

Each of these secondary anti-HBV efficacy endpoints will be analyzed in the same manner as described for the primary efficacy endpoint, except that stratification factors for the secondary efficacy endpoints include HBeAg status (positive vs. negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL).

The adverse events and clinical laboratory data will be summarized using descriptive statistics.

A total of approximately 240 HIV and HBV naïve, HIV-1 and HBV co-infected subjects, randomized in a 1:1 ratio to 2 treatment groups (120 subjects per treatment group), achieves 90% power to detect a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA-defined snapshot algorithm) difference between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have a response rate of 91% (based on Gilead Studies GS-US-380-1489 and GS-US-380-1490), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

A total of approximately 240 subjects also provides 81% power to detect a non-inferiority margin of 12% with respect to the co-primary efficacy endpoint of the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. This assumes that both treatment groups have a response rate of 88% (based on Gilead Studies GS-US-320-0108 and GS-US-320-0110), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
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
CPT	Child-Pugh-Turcotte
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
FTC/TAF	emtricitabine/tenofovir alafenamide , Descovy®
F/TDF	emtricitabine/tenofovir desoproxil 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
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
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

There is an urgent need to address HIV and HBV coinfection worldwide. Both HIV and HBV infection can lead to chronic disease, with attendant morbidity and mortality that is synergistically exacerbated by coinfection with both viruses.

Over 2 billion people are infected, 400 million chronically with Hepatitis B Virus, (HBV), which is a primary cause of chronic liver disease and a major contributor to mortality, contributing to half the burden of cirrhosis and hepatocellular carcinoma (HCC). HBV is endemic in parts of Asia and Africa, with 70% of the population showing serologic evidence of current or prior infection and approximately 8-15% with chronic hepatitis B infection {Kalayjian 2003}, {Drake 2004}, {Kourtis 2012}.

There are estimated to be 35 million people living with HIV/AIDS, with the majority in Asia and Africa; estimates ranging for a total of approximately 3-6 million individuals coinfected with HIV and HBV, coinfection rates are as high as 25% in areas where both viruses are endemic {Kourtis 2012}.

Coinfection worsens morbidity and mortality synergistically; HIV-HBV coinfected patients have higher HBV DNA levels and progress to chronic hepatitis B five times more quickly than HBV monoinfected patients and have higher risk of cirrhosis and HCC.

In HIV-positive patients co-infected with HBV, F/TDF or F/TAF are the preferred NRTI backbone of a fully suppressive antiretroviral regimen {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. For the majority of monoinfected chronic hepatitis B (CHB) subjects, life-long treatment is required as only a small percentage (< 10%) of subjects experience sustained loss of hepatitis B surface antigen (HBsAg), and as a consequence, achieve an effective cure of the disease. However, data in HIV/HBV coinfected patients are limited {Charpentier 2015}.

Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), has the potential to advance treatment of chronic hepatitis B infection, including those who are coinfected with HIV. In contrast to TDF, an oral prodrug that is rapidly cleaved by esterases in the intestines and plasma to TFV, TAF has been specifically synthesized to resist early enzymatic cleavage following oral administration and remain mostly intact until penetrating target cells. By virtue of this key distinguishing property, TAF when administered at a lower dose than TDF, is capable of efficiently delivering active drug (e.g. tenofovir diphosphate [TFV-DP]) to the cells where it is needed (e.g. HBV-infected hepatocytes, HIV-infected lymphoid cells) while systemic exposures of TFV are greatly reduced in comparison to oral administration of TDF 300 mg. In support of the concept of enhanced delivery of active drug for treatment of HBV, a study in dogs showed 70% of the orally administered TAF dose is extracted by the liver during first pass metabolism. Additionally, TAF has in vitro been shown to be efficiently taken up by hepatocytes where intracellular concentrations of TFV-DP are 120-fold higher with TAF compared with TFV, and

5-fold higher with TAF compared to TDF. These features are hypothesized to translate into the potential for effective suppression of viral replication and an improved tolerability and safety profile.

Bictegravir (GS-9883) is a potent inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infection. Antiviral testing has shown that bictegravir is active against a broad panel of HIV-1 viral lab strains and clinical isolates. Bictegravir is fully active against a panel of mutant viruses with resistance to NRTIs, 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 bictegravir.

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

1.2. Bictegravir (GS-9883, B)

1.2.1. General Information

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

1.2.2. Preclinical Pharmacology and Toxicology

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

1.2.2.1. Pharmacology

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

Bictegravir is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) and CYP3A. Bictegravir does not inhibit major human CYP isoforms or UGT1A1 at concentrations up to 25 μM. Consequently, bictegravir is unlikely to be a clinically relevant inhibitor of these enzymes, and is not expected to inhibit the metabolic clearance of drugs metabolized by these enzymes. Bictegravir only modestly inhibits renal transporter OCT2 (IC_{50} = 0.42 μM). As a result, bictegravir is not expected to significantly interfere with the key transporter responsible for creatinine tubular elimination at the clinically projected $C_{max.}$ Additionally, the risk that bictegravir will affect the OCT2-mediated excretion of co-administered drugs is considered to be low.

Bictegravir does not activate AhR and only weakly activates PXR at concentrations up to 50 μM (less than 5% and 40% of activation, respectively, compared to positive control compound). Therefore, bictegravir is not expected to act as an inducer through PXR- or AhR-mediated pathways at the doses and exposure levels projected in clinical use.

1.2.2.2. Toxicology

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

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

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

exhibited reversibility. There were no other adverse findings in the study, including clinical observations, or effects on body weight, body weight change, food consumption, ECGs, hematology, coagulation, clinical chemistry, urinalysis, and ophthalmoscopy.

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

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

1.2.3. Clinical Trials of Bictegravir

Clinical trials entailing the use of bictegravir include:

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

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

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

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

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

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

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

- GS-US-141-1485, a Phase 1 adaptive study to evaluate transporter, CYP-mediated and UGT1A1 drug-drug interactions between GS-9883 and probe drugs (completed)

- GS-US-141-1487, a Phase 1 randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate (completed)

- GS-US-311-1790, a Phase 1 Randomized, Open Label, Drug Interaction Study Evaluating the Effect of F/TAF FDC Tablet or GS-9883 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol (completed)

- GS-US-380-1761, a Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets (completed)

- GS-US-380-1991, a Phase I Single and Multiple Dose Study Evaluating the Pharmacokinetics, Safety, and Tolerability of GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/FTC/TAF) in Healthy Japanese and Caucasian Subjects (completed)

- GS-US-380-1999, a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate and Sofosbuvir/Velpatasvir/GS-9857 in Healthy Subjects (completed)

- GS-US-380-3908, a Phase 1, Blinded, Placebo-controlled, Two-period Crossover Drug Interaction Study to Assess the Effect of GS-9883/F/TAF on Metformin Pharmacokinetics in Healthy Subjects (completed)

- GS-US-380-3909, a Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on GS-9883 Pharmacokinetics (completed)

- GS-US-141-1475, a Phase 2 Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults (ongoing)

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

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

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

- GS-US-380-1878, a Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults (ongoing)

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

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

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

- GS-US-380-4449: A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching from an Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Regimen or a Tenofovir Disoproxil Fumarate Containing Regimen to Fixed-Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Elderly, Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 65 Years (ongoing)

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

1.2.3.1. Phase 1 Safety and Pharmacokinetics

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

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

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

Changes in serum creatinine were observed in this study, presumably via inhibition of the renal transporter OCT2. In the MAD cohorts (fasted), serum creatinine change at Day 14 ranged from 0.05 mg/dL for the 5 mg cohort to 0.18 mg/dL for the 300 mg/dL cohort. In Part D (DDI), conducted in the fed state (regular meal), subjects received 100 mg bictegravir monotherapy for 7 days and 100 mg bictegravir with F/TAF for 7 days, the mean serum creatinine change at Day 7 was 0.14 mg/dL following bictegravir and 0.17 mg/dL following bictegravir + F/TAF. All changes returned to baseline after discontinuation of bictegravir.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities included 10 subjects with Grade 3 urine dipstick tests for blood. All of these subjects were female, none of the labs were considered by the Investigator to be clinically significant, and all were associated with menstruation. No other Grade 3 or 4 laboratory abnormalities were observed.

Based on results in study GS-US-141-1218, pharmacokinetic profile of bictegravir was characterized by rapid absorption with time to peak plasma concentrations (median T_{max} of cohorts) ranging between 1 and 4 hours following administration under fasted conditions. bictegravir exposures were appropriately dose proportional following single dose 25-100 mg dose administration, with decreasing dose proportional at higher doses. The half-life of bictegravir was approximately 18 hours, with no changes observed across studied dose range as evidenced by parallel terminal phase slopes. A high-fat meal increased AUC_{inf} and C_{max} (geometric mean, 84% and 101%, respectively) following 100 mg single dose administration. Steady state was achieved after 4-6 days of once daily dosing of bictegravir with average accumulation ratios for AUC_{24hr} of 1.6.

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

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

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

Table 1-2 presents bictegravir plasma PK parameters following administration of bictegravir (5, 25, 50, 100, and 300 mg) once daily for 7 days. Following administration of either bictegravir (5, 25, 50, 100, or 300 mg) once daily for 7 days, the PK absorption profile observed on Days 1 and 7 was similar to that observed in Part A (SAD). The median T_{max} values ranged from 1.5 to 2.5 hours on Day 1 and 1.5 to 4.0 hours on Day 7. Linearity was observed comparing bictegravir AUC and C_{max} on Days 1 and 7 over the dose range of 25 to 50 mg. Steady state levels of bictegravir were achieved between Study Days 4 to 6 of dosing and maintained through Day 14. Accumulation is approximately 1.6-fold, which is consistent with the observed half-life of the bictegravir (approximately 18 hours).

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

		Multiple-Dose Bictegravir				
	Bictegravir PK Parameter Mean (%CV)[a]	5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 1	AUC_{0-24} (hr*ng/mL)	9033.6 (8.2)	27,775.1 (28.3)	58,371.4 (18.9)	79,773.8 (18.9)	180,714.3 (17.6)
	C_{max} (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T_{max} (hr)	1.50 (1.50, 1.50)	1.75 (1.00, 3.00)	1.50 (1.00, 2.00)	2.50 (2.00, 3.00)	2.50 (2.00, 4.00)

	Bictegravir PK Parameter Mean (%CV)[a]	Multiple-Dose Bictegravir				
		5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 7	AUC_{tau} (hr*ng/mL)	14,392.0 (16.7)	50,008.2 (26.6)	89,710.1 (22.7)	126,785.8 (23.7)	277,200.2 (16.7)
	C_{max} (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C_{tau} (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T_{max} (hr)	1.50 (1.00, 2.00)	3.00 (2.00, 3.00)	1.75 (1.50, 2.00)	1.75 (1.50, 3.00)	4.00 (2.00, 4.00)
	Accumulation Ratio of AUC (%)	160.5 (19.0)	182.2 (17.1)	154.0 (15.9)	158.5 (12.1)	157.5 (22.6)

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

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

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

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

CI = confidence interval; GLSM = geometric least squares mean

1.2.3.2. Phase 1b Proof of Concept

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

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

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

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

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

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

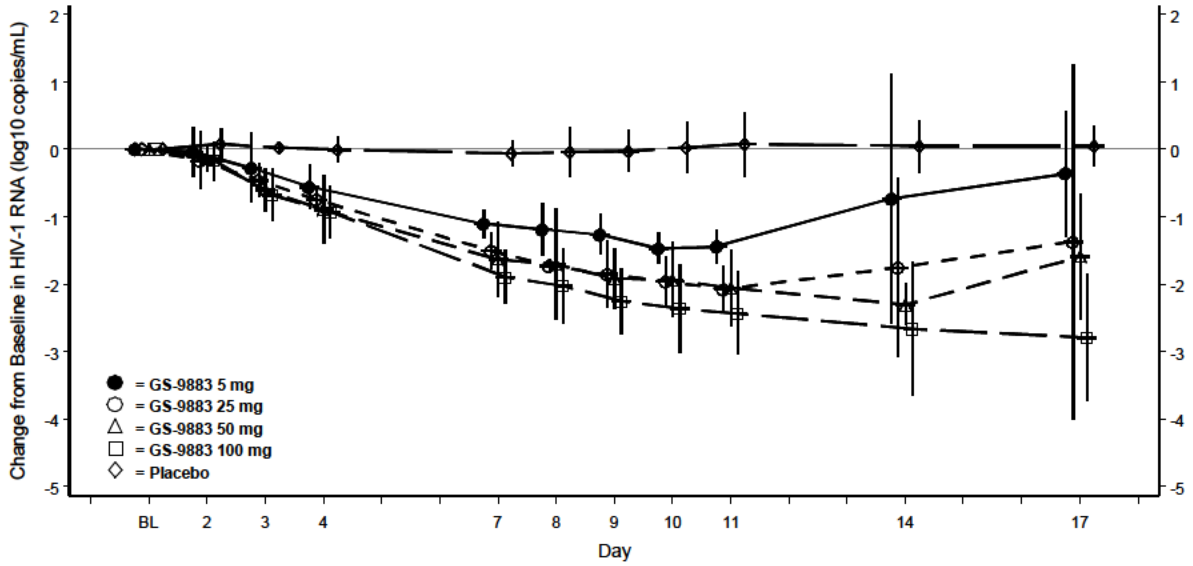
Table 1-4. Trough Bictegravir Plasma Concentrations at Steady State Following Bictegravir Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ_{95} Values (Bictegravir PK Analysis Set)

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

a The protein adjusted IQ95 (paIQ95) value is estimated based on steady-state Ctau values and the in vitro paIC95 value for wild-type HIV-1 (162 ng/ml).

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

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



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

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

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

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

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

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

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

Week 48 interim data are summarized below.

Subject Disposition and Baseline Characteristics

A total of 98 subjects were randomized and treated in the study: 65 subjects in the B+F/TAF group and 33 subjects in the DTG+F/TAF group. At the time of the Week 48 data analysis, 5 subjects (5.1%) had prematurely discontinued study drug, 3 in the B+F/TAF group and 2 in the DTG+F/TAF group. The reasons for study drug discontinuation were as follows (one subject each): AE, withdrawal of consent, and lost to follow-up in the B+F/TAF group, and noncompliance with study drug and lost to follow up in the DTG+F/TAF group.

Demographic and baseline characteristics were similar between the 2 treatment groups. Key baseline disease characteristics (ie, viral load, CD4+ cell count, and estimated glomerular filtration rate [eGFR]$_{CG}$) were similar between the 2 treatment groups.

Median (Q1, Q3) baseline HIV-1 RNA was 4.45 (3.96, 4.79) $\log_{10}$ copies/mL, with 82.7% having ≤ 100,000 copies/mL at baseline. Five subjects (5.1%) had > 400,000 copies/mL at baseline; of these, 4 subjects were randomized to B+F/TAF and 1 subject was randomized to DTG+F/TAF.

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

Efficacy Results

The primary efficacy endpoint was the proportion of subjects 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 subjects 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.

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were similar between the 2 treatment groups when assessed using the US FDA-defined snapshot algorithm based on the full analysis set (FAS) (Table 1-5), as follows: B+F/TAF 96.9%; DTG+F/TAF 90.9%; difference in percentages: 6.4%, 95% CI: −6.0% to 18.8%.

As expected for an INSTI-containing regimen, HIV-1 RNA levels decreased rapidly in the first 4 weeks following initiation of study drug in both treatment groups. After Week 4, HIV-1 RNA values were stable and similar between the 2 treatment groups through Week 48; mean (SD) decreases from baseline at Week 48 using the FAS were as follows: B+F/TAF −3.09 (0.752) $\log_{10}$copies/mL; DTG+F/TAF −3.11 (0.852) $\log_{10}$copies/mL; difference in least-squares mean (LSM): −0.06 $\log_{10}$copies/mL, 95% CI: −0.32 to 0.20 $\log_{10}$ copies/mL.

The mean (SD) increases from baseline in CD4+ cell counts were similar between the 2 treatment groups through Week 48 using the FAS, as follows: B+F/TAF 258 (221.7) cells/µL; DTG+F/TAF 192 (242.0) cells/µL; difference in LSM: 72 cells/µL, 95% CI: −30 to 174 cells/µL.

Table 1-5. GS-US-141-1475: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	B+F/TAF (N = 65)	DTG+F/TAF (N = 33)	B+F/TAF vs DTG+F/TAF	
			p-value[a]	Difference in Percentages (95% CI)[b]
HIV-1 RNA < 50 copies/mL	63 (96.9%)	30 (90.9%)	0.17	6.4% (−6.0% to 18.8%)
HIV-1 RNA ≥ 50 copies/mL	1 (1.5%)	2 (6.1%)		
HIV-1 RNA ≥ 50 copies/mL in Week 48 window	0	1 (3.0%)		
Discontinued study drug due to lack of efficacy	0	0		
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL[c]	1 (1.5%)	1 (3.0%)		
No virologic data in Week 48 window	1 (1.5%)	1 (3.0%)		
Discontinued study drug due to AE/death	1 (1.5%)	0		
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[c]	0	1 (3.0%)		
Missing data during window but on study drug	0	0		

Week 48 window was between Day 295 and 378 (inclusive).
a p-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).
b Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel proportion.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Interim Virology Resistance Data

Through Week 48, no emergent drug resistance was detected in the B+F/TAF group.

Safety Results

Adverse Events

Adverse events were reported in 84.6% (55 of 65 subjects) in the B+F/TAF group and 66.7% (22 of 33 subjects) in the DTG+F/TAF group. The most commonly reported AEs by treatment group were as follows:

- B+F/TAF group—diarrhea (12.3%, 8 of 65 subjects); and headache, nausea, and upper respiratory tract infection (each 7.7%, 5 subjects)
- DTG+F/TAF group—diarrhea and nausea (each 12.1%, 4 of 33 subjects); and arthralgia, fatigue, flatulence, furuncle, gastroenteritis, costochondritis, hemorrhoids, and pruritus (each 6.1%, 2 subjects)

The majority of AEs were Grade 1 in severity, with similar incidence of Grade 2, 3, or 4 AEs between the 2 treatment groups. Grade 3 AEs were uncommon, with all Grade 3 AEs reported in the B+F/TAF group (6.2%, 4 subjects); only 1 Grade 3 AE was considered related to study drug by the investigator (urticaria in a B+F/TAF subject). No individual Grade 3 AE was reported for > 1 subject. No Grade 4 AEs were reported.

Serious AEs were uncommon, with all reported SAEs occurring in the B+F/TAF group (4.6%, 3 subjects). No SAE was considered related to study drug by the investigator. The SAEs reported were appendicitis, psychotic disorder/suicidal ideation, and diabetic ketoacidosis.

The incidence of AEs considered related to study drug by the investigator was similar between the 2 treatment groups (B+F/TAF 20.0%, 13 subjects; DTG+F/TAF 21.2%, 7 subjects). Nearly all study drug-related AEs were Grade 1 in severity, with similar incidence of Grade 2, 3, or 4 study drug-related AEs between the 2 treatment groups (B+F/TAF 3.1%, 2 subjects; DTG+F/TAF 3.0%, 1 subject). The only Grade 3 study drug-related AE reported (urticaria in a B+F/TAF subject) was also the only AE leading to premature study drug discontinuation; the event began on Day 130 and led to discontinuation of study drug on Day 162.

No deaths or pregnancies were reported in either treatment group.

Clinical Laboratory Evaluations

Most subjects in both treatment groups had at least 1 laboratory abnormality (B+F/TAF 84.4%, 54 of 64 subjects; DTG+F/TAF 87.5%, 28 of 32 subjects). Most of the reported laboratory abnormalities were Grade 1 or 2 in severity. The incidence of Grade 3 or 4 laboratory abnormalities was similar between the 2 treatment groups (B+F/TAF 25.0%, 16 subjects; DTG+F/TAF 21.9%, 7 subjects).

Graded laboratory abnormalities in ALT and aspartate aminotransferase (AST) were reported more frequently and with greater severity in the B+F/TAF group than in the DTG+F/TAF group. Graded ALT abnormalities were reported in 23.4% (15 of 64 subjects) in the B+F/TAF group and 9.4% (3 of 32 subjects) in the DTG+F/TAF group, and graded AST abnormalities were

reported in 20.3% (13 of 64 subjects) in the B+F/TAF group and 9.4% (3 of 32 subjects) in the DTG+F/TAF group. Grade 3 ALT elevations occurred in 1 subject in the B+F/TAF group and none in the DTG+F/TAF group. Grade 3 AST elevations were seen in 3 subjects in the B+F/TAF group (one of whom also had a Grade 3 ALT elevation) and none in the DTG+F/TAF group. Of the 3 subjects who had Grade 3 transaminase elevations, 2 were associated with simultaneous Grade 4 CK elevations, were transient, and resolved rapidly without any associated AEs. One participant had both Grade 3 AST and ALT persistent elevations that were attributed to ongoing alcohol use. No Grade 4 transaminase elevations were observed in either treatment group.

Grade 3 or 4 CK elevations were seen in 9.4% (6 of 64 subjects) in the B+F/TAF group and in 3.1% (1 of 32 subjects) in the DTG+F/TAF group. All of the Grade 3 or 4 CK elevations occurred in young men (age range, 24 to 31 years), were transient, and resolved without treatment interruption, and none of these laboratory abnormalities were associated with AEs.

There were similar increases from baseline in median (Q1, Q3) serum creatinine in both treatment groups at Week 48: B+F/TAF 0.08 (0.02, 0.15) mg/dL; DTG+F/TAF 0.12 (0.02, 0.20) mg/dL. There were decreases in median (Q1, Q3) $eGFR_{CG}$ at Week 48, which were smaller in the B+F/TAF than in the DTG+F/TAF group: B+F/TAF −7.0 (−18.7, 1.6) mL/min; DTG+F/TAF −11.3 (−24.5, −0.8) mL/min.

There were no clinically significant changes from baseline or differences between treatment groups in the median values for hematology, chemistry, or metabolic parameters.

Conclusions

Key conclusions from Study GS-US-141-1475 at Week 48 include the following:

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were similar between the 2 treatment groups when assessed using the US FDA-defined snapshot algorithm based on the FAS, as follows: B+F/TAF 96.9%; DTG+F/TAF 90.9%; difference in percentages: 6.4%, 95% CI: −6.0% to 18.8%. There was a similar increase in the mean (SD) CD4+ cell count between the 2 treatment groups: B+F/TAF 258 (221.7) cells/μL; DTG+F/TAF 192 (242.0) cells/μL; difference in LSM: 72 cells/μL, 95% CI: −30 to 174 cells/μL.

- 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.

  — The most commonly reported AEs were diarrhea (12.3%, 8 of 65 subjects); and headache, nausea, and upper respiratory tract infection (each 7.7%, 5 subjects) in the B+F/TAF group, and diarrhea and nausea (each 12.1%, 4 of 33 subjects); and arthralgia, fatigue, flatulence, furuncle, gastroenteritis, costochondritis, hemorrhoids, and pruritus (each 6.1%, 2 subjects) in the DTG+F/TAF group.

— One subject discontinued study drug due to AE: Grade 3 urticaria beginning on Day 130 in a B+F/TAF subject. There were SAEs in 3 subjects, none of which were considered related to study drug by the investigator, or led to study drug discontinuation.

— The percentage of subjects with at least 1 treatment-emergent laboratory abnormality was similar between treatment groups. The majority of treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity. Graded laboratory abnormalities in ALT and AST were reported more frequently and with greater severity in the B+F/TAF group than in the DTG+F/TAF group.

There were similar increases from baseline in serum creatinine in both treatment groups at Week 48. The decrease from baseline in $eGFR_{CG}$ was smaller in the B+F/TAF group than in the DTG+F/TAF group.

1.2.3.4. Summary of Phase 3 Studies

GS-US-380-1489

Results from a blinded phase 3 study were reported that compared B/F/TAF FDC to co-formulated abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC, Triumeq®) {Gallant 2017}. HIV-infected, treatment-naïve, HLA-B*5701-negative, HBV-uninfected adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min were randomized 1:1 to receive blinded treatment with fixed-dose combination B/F/TAF (50/200/25 mg) or ABC/DTG/3TC (600/50/300 mg) with matching placebos once daily. The primary endpoint was proportion of participants with HIV-1 RNA (VL) < 50 c/mL at W48 (FDA snapshot). Noninferiority was assessed through 95.002% confidence intervals (CI) (12% margin). Secondary endpoints were safety (adverse events [AEs] and laboratory abnormalities) and pre-defined analyses of changes from baseline in bone mineral density (BMD) and measures of renal function, including eGFR and proteinuria. Six hundred and twenty nine participants were randomized and treated (314 B/F/TAF, 315 ABC/DTG/3TC): 10% women, 36% Black, 16% VL >100,000 c/mL, 11% CD4 < 200 cells/mL. Median baseline characteristics: age 32 yrs, CD4 count 444 cells/μL, and VL 4.47 $\log_{10}$ c/mL. At W48, B/F/TAF was noninferior to ABC/DTG/3TC, with 92.4% on B/F/TAF and 93.0% on ABC/DTG/3TC achieving HIV-1 RNA < 50 c/mL (difference -0.6%; 95.002%CI -4.8% to 3.6%, p=0.78). No resistance mutations emerged in either group. Comparing B/F/TAF to ABC/DTG/3TC throughout, the most common AEs were diarrhea (13%, 13%), headache (11%, 14%), and nausea (10%, 23%). Few participants (0 vs 4 [1%]) had any AEs leading to premature study drug discontinuation. At W48, mean % changes from baseline in BMD were -0.83% vs. -0.60% (p=0.39) [lumbar spine] and -0.78% vs. -1.02% (p=0.23) [total hip]. No differences between treatments were noted in changes from baseline for eGFR and proteinuria at W48. At W48, B/F/TAF achieved virologic suppression in 92.4% of treatment-naïve adults and was noninferior to ABC/DTG/3TC, with no emergent resistance. B/F/TAF was safe and well tolerated with less nausea than ABC/DTG/3TC. Bone and renal safety profiles were similar between groups.

GS-US-380-1490

A second phase 3 study compared bictegravir and DTG, each with F/TAF, utilizing a single-pill co-formulation of B/F/TAF {Sax 2017}. Treatment-naïve, HIV-infected adults with estimated glomerular filtration rate (eGFR) ≥30 mL/min were randomized 1:1 to receive blinded treatment with fixed dose combination B/F/TAF (50/200/25 mg) or DTG (50 mg) + F/TAF (200/25 mg) with matching placebos once daily through W48. Chronic hepatitis B and/or C infection was allowed. The primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL (c/mL) at W48 (FDA snapshot). Noninferiority was assessed through 95.002% confidence intervals (CI) using a margin of 12%. Secondary endpoints were safety measures (adverse events [AEs] and laboratory results). There were 645 participants randomized and treated (320 B/F/TAF, 325 DTG + F/TAF): 12% women, 31% Black, 19% viral load (VL) >100,000 c/mL, 12% CD4 < 200 cells/μL, median age 34 yrs, CD4 count 440 cells/μL, and VL 4.44 $\log_{10}$ c/mL. At W48, B/F/TAF was noninferior to DTG + F/TAF, with 89.4% on B/F/TAF and 92.9% on DTG + F/TAF achieving HIV-1 RNA < 50 c/mL (difference -3.5%; 95.002%CI -7.9% to 1.0%, p=0.12). Six subjects discontinued treatment for the following reasons: patient decision-3, protocol violation due to incarceration-1, lost to follow-up-1 and investigator discretion-1. Both the Missing=Excluded (M=E) and Missing=Failure (M=F) sensitivity analyses were pre-specified M=E analysis (B/F/TAF vs DTG + F/TAF, % treatment difference (95% CI); p-value): 99.0% (288/291) vs. 99.3% (304/306), -0.4% (-2.3, 1.6); p=0.63 Missing values represent a potential source of bias in a clinical trial. Therefore, the study protocol pre-specified the M=E analysis as one imputation method for missing data The M=E population analysis excludes subjects in the full analysis set who do not have HIV-1 RNA data at the efficacy analysis time point. Of note, the M=E analysis set includes subjects with HIV-1 RNA data at the efficacy analysis time point, even if the subject has discontinued study antiretroviral medications but remained “in the study” on non-study antiretroviral medications (for the treatment of HIV). M=F analysis (B/F/TAF vs DTG + F/TAF, % treatment difference (95% CI); p-value): 90.0% (288/320) vs. 93.5% (304/325), -3.4% (-7.7, 0.9); p=0.12 The study protocol pre-specified the M=F analysis as a 2nd imputation method for missing data The M=F population considers subjects in the full analysis set who do not have HIV-1 RNA data at the efficacy analysis time point as having HIV-1 RNA ≥ 50 copies/mL. Of note, the M=F analysis set includes subjects with HIV-1 RNA data at the efficacy analysis time point, even if the subjects has discontinued study antiretroviral medications but remained “in the study” on non-study antiretroviral medications (for the treatment of HIV). At W48, proportion of participants with HIV-1 RNA ≥50 c/mL was < 1% in each arm. No study subject in either treatment arm developed resistance to any of the study drugs. The most common AEs were headache (13% B/F/TAF, 12% DTG + F/TAF) and diarrhea (12% for both). Few participants (5 [2%], 1 [< 1%]) had AEs leading to premature study discontinuation. Lipid changes were not significantly different between study arms. No renal discontinuations and no cases of proximal renal tubulopathy were reported. After 48 weeks, B/F/TAF achieved virologic suppression in 89.4% of treatment- naïve adults and was noninferior to DTG + F/TAF. B/F/TAF was safe and well tolerated.

1.3. Information about Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada®, (F/TDF))

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

1.4. Information about Dolutegravir (DTG, Tivicay®)

An ongoing observational study in Botswana identified neural tube defects (NTDs) in infants born to four of 426 women who started DTG prior to pregnancy, and were on it at the time of conception. The incidence rate for NTDs in these infants was 0.9%, while the reported rate of NTDs for HIV-infected women on non-DTG-containing regimen was 0.1%. These preliminary results suggest that women who received DTG at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these embryonic defects.

The following guidance has been issued regarding the use of DTG in women who are pregnant, who become pregnant, or are of child bearing potential.

- FDA statement: https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm
- U.S. DHHS Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential
- European Medicines Agency (EMA): http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1

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

1.5. Rationale for This Study

B/F/TAF has demonstrated efficacy and safety in Phase 2 and Phase 3 studies in HIV-monoinfected patients. TAF 25 mg has been evaluated in two global Phase 3 HBV monoinfection studies – one each in treatment naïve and experienced HBeAg-negative subjects (GS-US-320-0108) and HBeAg-positive subjects (GS-US-320-0110) and is approved for the treatment of hepatitis B infection.

Currently, TAF and TDF are approved by the US FDA for treatment of HBV- infected patients. This study will examine the efficacy and safety of B/F/TAF versus DTG +F/TDF in HBV and HIV-co-infected patients. Current guidelines for treatment of HBV in HIV co-infected patients emphasize the need to treat co-infected patients due to higher rates of liver disease progression. Both TDF and TAF containing regimens are recommended in multiple guidelines for treatment of HBV in HIV-1 infected patients {Gunthard 2016}, {Gorden 2007}, {Terrault 2016}, {European Association for the Study of the Liver 2017}, {European AIDS Clinical Society (EACS) 2016}, and {Sarin 2016}. The evaluation of the safety and tolerability of B/F/TAF in HIV and HBV coinfected patients is highly clinically relevant.

1.6. Risk/Benefit Assessment for the Study

HIV and HBV co-infection worsens morbidity and mortality synergistically; co-infected patients have higher risk of cirrhosis and hepatocellular carcinoma. In HIV-positive patients co-infected with HBV, F/TDF or F/TAF are the preferred NRTI backbone of a fully suppressive antiretroviral regimen {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. This study seeks to generate safety and efficacy data of B/F/TAF FDC in this population by enrolling treatment naïve patients. The comparator regimen contains DTG and F/TDF, a fully suppressive regimen. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis. The risk of class effects is considered to be low. Potential benefits may include provision of a new ARV therapy to patient population that may have fewer side effects than alternative therapies. Other potential benefits include provisions of fixed dose combination therapy, and the knowledge that patient participation will contribute to the body of knowledge of HIV therapies.

In summary, the risk/benefit for this study is acceptable due to the following considerations:

- Treatment of HBV is indicated and important in all HIV co-infected patients due to accelerated progression of liver disease
- TDF and TAF are approved for the treatment of HBV infection
- B/F/TAF has been proven to be safe, well tolerated and effective in the treatment of HIV-infected patients
- Hepatic flares, defined by an increase in ALT of five-fold above upper limit of normal, are not uncommon early in treatment initiation and will be closely monitored (refer to Section 7.5.4)
- Risk of nephrotoxicity, defined as a decreased in eGFR < 50ml/min is considered to be low and will be closely monitored (refer to Section 7.5.5)

The benefit-risk assessment for this study is favorable at this time.

1.7. Rational 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}.

DTG + F/TDF

The 50 mg dose of DTG represents the approved, marketed dose for this agent that is currently available as a single agent, Tivicay® and as a component of the FDC, Triumeq®. Within the FDC, F/TDF, the 200 mg dose of FTC and the 300 mg dose of TDF represent the approved marketed doses for these agents that are currently available as single agents (EMTRIVA and VIREAD) and as a component of a number of FDCs, including: ATRIPLA, COMPLERA (EVIPLERA), and STRIBILD. 300 mg dose of TDF in Truvada® is the dose approved for the treatment of HBV monoinfection, and is the dose recommended for the treatment of HIV/HBV coinfection by multiple treatment guidelines {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}.

1.8. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF in HIV and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48
- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF in HIV and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48

The secondary objectives of this study are:

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 96
- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96
- To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with ALT normalization at Weeks 48 and 96
- To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with HBsAg loss at Weeks 48 and 96
- To evaluate the safety and tolerability of the two treatment groups through Week 96

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints are:

- The proportion of subjects that have HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm
- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 by Missing = Failure approach

The secondary anti-HIV efficacy endpoints are:

- The proportion of subjects that have HIV-1 RNA < 50 copies/mL at Week 96
- The change from baseline in CD4 cell count and CD4% at Weeks 48 and 96

The secondary anti-HBV efficacy endpoints are:

- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96
- The proportion of subjects with ALT normalization at Weeks 48 and 96
- The proportion of subjects with HBsAg loss at Weeks 48 and 96

3.2. Study Design

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

3.3. Study Treatments

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

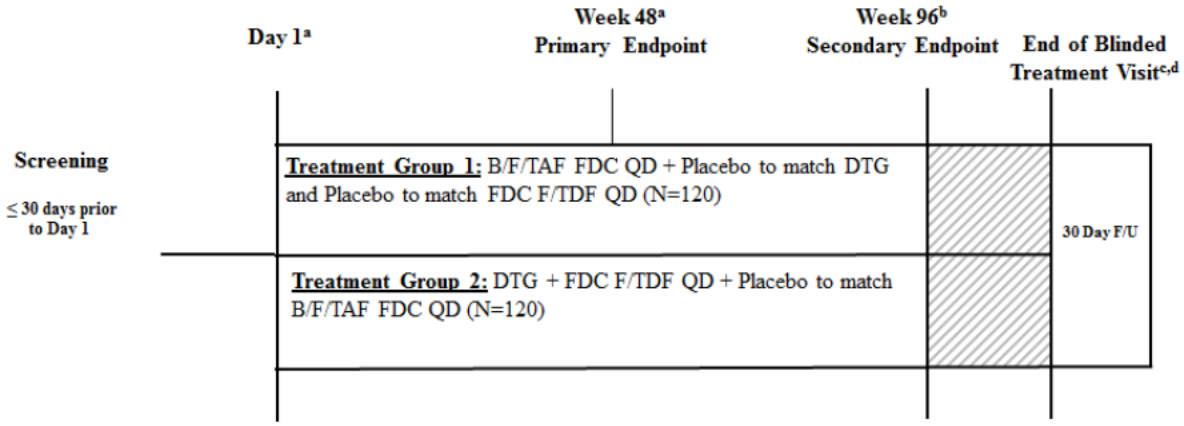
Treatment Group 1 (n=120): FDC of bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + placebo to match dolutegravir 50 mg (DTG) and placebo to match FDC of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (F/TDF) administered orally, once daily, without regard to food

Treatment Group 2 (n=120): dolutegravir 50 mg (DTG) + FDC of emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg (F/TDF) + Placebo to match FDC of bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food

Randomization will be stratified by HBeAg (positive vs. negative), HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL), CD4+ cell count (< 50 cells/μL vs. ≥ 50 cells/μL) at Screening.

3.4. Duration of Treatment and End of Study

Subjects will be treated for at least 96 weeks. Following the Screening and Day 1 visits, subjects will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks from Week 12 through Week 96. Once all subjects complete their Week 96 visit and Gilead completes the Week 96 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected subjects following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open label (OL) extension phase until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.



a Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 96.

b After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit.

c Once the last subject completes their Week 96 visit and Gilead completes the Week 96 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected subjects following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open label extension or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

d Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label rollover extension phase will be required to return to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

CCI [redacted]

[redacted]

[redacted]

CCI

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 240 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

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

2) Age ≥ 18 years

3) HIV-1 co-infection:

   a) Must be HIV antiretroviral treatment naive with plasma HIV-1 RNA ≥ 500 copies/mL at screening

   b) ≤ 10 days of prior therapy with any antiretroviral agent, including lamivudine and entecavir, following a diagnosis of HIV-1 infection (except the use for PrEP or PEP, up to one month prior to screening)

   c) Screening genotype report must show sensitivity to FTC and TFV. This report will be provided by Gilead Sciences. Alternatively, if genotype results from a local laboratory obtained ≤ 90 days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed

4) HBV co-infection:

   a) Must be HBV treatment naïve (defined as < 12 weeks of oral antiviral treatment)

   b) Screening HBV DNA ≥ 2000 IU/mL

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

6) 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:

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

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

7) Hepatic transaminases (AST and ALT) ≤ 10 × upper limit of normal (ULN)

8) Total bilirubin ≤ 2.5 × upper limit of normal (ULN)

9) Adequate hematologic function (absolute neutrophil count ≥ 750/mm3 (≥ 0.75 GI/L); platelets ≥ 50,000/mm3 (≥ 50 GI/L); hemoglobin ≥ 8.5 g/dL (≥ 85 g/L))

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

11) Female subjects of childbearing potential and male subjects who are fertile who engage in heterosexual intercourse must agree to utilize protocol specified method(s) of contraception as described in Appendix 6.

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

4.3. Exclusion Criteria

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

1) Hepatitis C Virus (HCV) antibody positive and HCV RNA detectable

2) Previous use of any approved or experimental HIV integrase inhibitor

3) An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to Appendix 7)

4) Subjects experiencing decompensated cirrhosis (eg, ascites, encephalopathy, or variceal bleeding) or with Child-Pugh-Turcotte (CPT) C impairment

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

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

7) 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

8) Active, serious infections (other than HIV-1 and HBV infection) requiring parenteral 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 subject unsuitable for the study or unable to comply with the dosing requirements

11) Any known allergies to the excipients of B/F/TAF FDC or DTG + F/TDF FDC tablets

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

13) Females who are breastfeeding

14) Subjects receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with FTC, TAF, TDF, bictegravir and DTG

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
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, echinacea

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

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

16) Active tuberculosis infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

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

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

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

Randomization will be stratified by HBeAg (positive vs. negative), HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL), CD4+ cell count (< 50 cells/μL vs. ≥ 50 cells/μL) at screening.

The IWRS will assign study drug bottle numbers of blinded FDC of B/F/TAF + placebo to match DTG + placebo to match F/TDF FDC, or DTG + F/TDF FDC + placebo to match FDC of B/F/TAF at each study visit for each subject.

At the End of Blinded Treatment Visit the IWRS will assign open label FDC of B/F/TAF.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, or in the case of pregnancy that occurs while on study drug, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care or in the event of a pregnancy that occurs while on

study drug. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

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

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

5.2. Description and Handling of Study Drug

5.2.1. Formulation

5.2.1.1. Bictegravir/Emtricitabine/Tenofovir alafenamide (B/F/TAF) 50/200/25 mg and Placebo to Match Tablets

B/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. 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.

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

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

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

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

5.2.1.3. Emtricitabine/Tenofovir disoproxil fumarate (F/TDF) 200 mg/300 mg and Placebo to Match Tablets

F/TDF tablets are capsule-shaped, film-coated blue, debossed with "GILEAD" on one side of the tablet and plain-faced on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. In addition to the active ingredients, the F/TDF tablets contain croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablet cores are film-coated with lactose monohydrate, hypromellose, triacetin, titanium dioxide, and FD&C Blue#2.

The placebo to match F/TDF tablets are capsule-shaped, film-coated blue, debossed with "GILEAD" on one side of the tablet and plain-faced on the other side of the tablet. PTM F/TDF tablets are identical in physical appearance to F/TDF tablets. The placebo tablet cores contain lactose monohydrate, croscarmellose sodium, pregelatinized starch, denatonium benzoate, and magnesium stearate. The tablet cores are film-coated with lactose monohydrate, hypromellose, triacetin, titanium dioxide, and FD&C Blue#2.

5.2.2. Packaging and Labeling

5.2.2.1. Bictegravir/Emtricitabine/Tenofovir alafenamide (B/F/TAF) 50/200/25 mg and Placebo to Match Tablets

B/F/TAF tablets and PTM 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.

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

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

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

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

5.2.2.3. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) 200 mg/300 mg and Placebo to Match Tablets

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

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

5.2.3. Storage and Handling

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

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. 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 Bictegravir/Emtricitabine/Tenofovir alafenamide and Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate

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

Treatment Group 1: FDC of bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + placebo to match dolutegravir 50 mg (DTG) and placebo to match FDC of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (F/TDF) administered orally, once daily, without regard to food

Treatment Group 2: dolutegravir 50 mg (DTG) + FDC of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (F/TDF) + placebo to match FDC of bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food.

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

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

5.4. Prior and Concomitant Medications

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

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

Table 5-1. Prior and Concomitant Medications

Drug Class	Agents Disallowed*	Use Discouraged and To Be Used With Caution
Acid Reducing Agents Antacids Buffered medications		Concentration of study drug may decrease with antacids. Administer study drug 2 hours before or 6 hours after taking antacids (e.g., Tums or Rolaids); the ulcer medication sucralfate (Carafate); or vitamins or mineral supplements that contain calcium, iron or zinc.
Antiarrhythmic Agent	Dofetilide	
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinacea	
Oral Hypoglycemic Agent		Close monitoring of metformin use is recommended. A dose adjustment of Metformin may be necessary. Limit total daily doses of metformin to 1000 mg when initiating study medication or if initiating metformin while on study drug.

5.5. Accountability for Investigational Medical Product (IMP)

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

Study Drug accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits
- Record the date, subject number, subject initials, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Study drug return and disposal will be performed as outlined in Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in this section and in tabular form in Appendix 2 and Appendix 3.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

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

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent
- Obtain medical history including history of HIV-1 disease-related events and prior medications within 30 days of the screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- 12-lead ECG performed supine
- Height
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Review of adverse events and concomitant medications

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30-days after screening for the Day 1 Visit.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events electronic case report form

(eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF (Section 7).

6.3. Randomization

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

6.4. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. **The Investigator must have received the results from the screening genotype report and confirmed eligibility before proceeding with the Day 1 visit.** The subject must complete all study procedures before being administered the study drug:

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Provide subject dosing diary to all subjects for PK collection
- Dispense study drug
- Observed first dose administration of the assigned study drugs as described in Section 5.3.
- Subjects should be instructed to take study drugs without regard to food. The subject should be counseled regarding the importance of adherence and taking their study medications at approximately the same time each day as directed by the Investigator.

6.5. Treatment Assessments (Week 4 – 96)

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

Study visits are to be completed within ± 2 days of the protocol-specified visit date (based on the Day 1 visit) through Week 12 and completed within ± 6 days of the protocol-specified visit date through Week 96, unless otherwise specified. The visit window at Weeks 48 and 96 will be ± 6 weeks of the protocol-specified visit date, and this clinical visit window coincides with the Weeks 48 and 96 statistical analysis window for HIV-1 RNA.

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

- Review of AEs and changes in concomitant medications
- Complete physical examination **(Weeks 24, 48, 96)** (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 Section 6.10
- Provide subject dosing diary to all subjects **(Weeks 4, 8, 12 and 24)**
- Dosing diaries will be collected from subjects for the trough and post-dose PK blood sample collection as noted in Section 6.10. If a dosing diary is not returned the site may ask the subject for the time of the last dose and if it was taken with or without food.
- Document study drug dispensation and accountability for all study drugs dispensed.

6.6. Treatment Assessments (Post Week 96 until the End of Blinded Treatment Visit)

6.6.1. Post Week 96 Assessments

After Week 96, all subjects will continue to take their blinded study drugs and attend visits every 12 weeks until the last subject completes the Week 96 visit of the blinded phase. 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 **(every 48 weeks)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Document study drug dispensation and accountability for all study drugs dispensed.

6.6.2. End of Blinded Treatment Visit Assessments

Once the last subject completes their Week 96 visit and Gilead completes the Week 96 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected subjects following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open label extension phase for up to 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

Subjects who receive the open-label B/F/TAF FDC will return for study visits every 12 weeks.

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

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

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

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Document study drug dispensation, if applicable, and accountability for all study drugs dispensed
- Subjects who wish to continue in the Open-Label Rollover extension study will receive open label B/F/TAF.

6.7. Open-Label Rollover Extension Assessments

For purposes of study visit identification during the open-label rollover extension, study visits will be identified by the number of weeks that have elapsed between the End of Blinded Treatment Visit and the corresponding open-label study visit, and labeled with “OL” (Week 12 OL, Week 24 OL, Week 36 OL, etc.).

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

Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the End of Blinded Treatment Visit through Week 12 OL and completed ± 6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified.

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

- Review of AEs and changes in concomitant medications
- Complete physical examination **(every 48 weeks)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Document study drug dispensation and accountability for all study drugs dispensed.

6.8. Post-Treatment Assessments

6.8.1. Early Study Drugs Discontinuation Assessments

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

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

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

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

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

- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.10
- Drug accountability

6.8.2. 30 Day Follow-Up Visit

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

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

Subjects who complete the study through the End of Blinded Treatment Visit, and refuse to participate in the open-label rollover extension will be required to return to the clinic 30 days after the completion of study drug for the 30 Day Follow-Up Visit.

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

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

For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 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 Section 6.10

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

6.9. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

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

Note: Female subjects who become pregnant during the study will be discontinued from the study and their study treatment assignment will be unblinded by the investigator and shared with the subject.

- Development of active tuberculosis infection

Study medication may be discontinued in the following instances:

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

6.10. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below and in Appendix 2 and Appendix 3.

6.10.1. Blood Samples

Blood samples will be collected at all study visits (including the open-label rollover extension phase), unless otherwise noted for the below noted laboratory analyses:

- Serum pregnancy test at the Screening Visit (females of childbearing potential only). If the test is positive, the subject will not be enrolled. At all subsequent study visits, serum pregnancy test will be performed if urine pregnancy test is positive.

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

  — At Day 1, Weeks 24, 48, 72, 96, every 24 weeks after Week 96, End of Blinded Treatment Visit, and every 24 weeks after the End of Blinded Treatment Visit in the open label extension phase glucose will be done as part of the fasting metabolic assessments and not part of the chemistry profile.

  — PT/INR (prothrombin time/international normalized ratio) will be analyzed at Screening and Day 1 Visits.

- 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) at Day 1, Weeks 24, 48, 72, 96, every 24 weeks after Week 96, End of Blinded Treatment Visit, and every 24 weeks after End of Blinded Treatment Visit in the open label rollover extension phase. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

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

  — If eGFR is < 50 mL/min at Day 1 visit, Cystatin C will be measured

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

- CD4+ cell count and CD4%

- Plasma HIV-1 RNA

- Hepatitis B Virus (HBV) blood panel:

  — HBV serologies: HBsAg, reflex anti-HBs Ab, HBeAg, reflex anti-HBe Ab

  (Screening, Day 1 and Weeks 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks after Week 96 until the End of Blinded Treatment Visit. In the open-label extension phase, testing will be completed every 48 weeks)

- Plasma HBV DNA will be monitored at all study visits.

- Plasma sample for HBV Genotyping (A-H) at Day 1 visit.

- Serum samples for potential sequence analysis of HBV polymerase/reverse transcriptase (pol/RT) should be collected at all time points except screening. Sequencing analysis of the HBV pol/RT will be attempted for all subjects who remain viremic (HBV DNA ≥ 69 IU/mL) at Weeks 48, 96 and Early Study Drug Discontinuation Visit as early as Week 8 and according to Section 6.15.

- Hepatitis C virus (HCVAb) serology at Screening, Weeks 48, 96, every 48 weeks after Week 96 and every 48 weeks in the open label rollover extension phase. Subjects who are HCVAb positive will have a HCV RNA test performed.

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

- Sample collection for resistance testing for subjects who meet the criteria for HIV-1 virologic failure will be managed according to the Management of Virologic Rebound Section 6.14.

- Trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4, 12, and 36.

  — Subject must be instructed to not take their study drugs on the morning of their visit for the trough sample collection. If the subject has taken their dose of study drugs prior to the visit, the visit may proceed, but the subject must return within 72 hours for the trough PK sample collection.

- Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose at Weeks 8 and 24.

  — In the event a subject routinely takes their study drug in the evening, the subject will not be instructed to change their dosing time, or participate in the observed dose. A single PK sample will be collected at Weeks 8 and 24. Time of sample collection will be recorded in the source documents and the subject will be asked to confirm the time of the last dose, which will also be recorded in the source documents.

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

- Whole blood storage sample for safety, virology, or PK testing at Day 1, Week 48 and Week 96. This sample is not optional.

[redacted]

6.10.2. Urine Samples

Urine samples will be collected at all study visits, unless otherwise noted for the below noted laboratory analyses:

- Urinalysis

- Urine pregnancy testing for females of childbearing potential only (not collected at Screening and 30 Day-Follow-up Visit). Positive urine pregnancy tests will be confirmed with a serum test. If the serum test is positive, the subject will be discontinued.
- Markers of renal dysfunction (collected fasted): If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to provide a urine sample for markers of renal dysfunction at Day 1 Visit, Weeks 24, 48, 96 and ESDD (if applicable).

6.10.3. Blood Storage Samples

Any residual blood samples from the samples collected will be frozen and stored. These stored blood samples may be used by the Sponsor or its research partners for HIV-1 and/or HBV or related diseases, genotyping/phenotyping assays or their development, for retesting the amount of HIV-1 and/or HBV in the blood, for measurement of antiviral drug levels in the blood, or for testing to learn more about how the study drug has worked against HIV-1 and/or HBV or related diseases, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study subjects. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences for a period up to 15 years.

6.11. Assessments for Premature Discontinuation from Study

If a subject discontinues study drug in the blinded phase of the study (for example, as a result of an AE), every attempt should be made to keep the subject in the study, and continue to perform the required study procedures until the End of Blinded Treatment Visit. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.12. End of Study

End of study is defined as completion of the 96 weeks of treatment and the 30 Day Follow-Up visit. Subjects that enter the extension phase will complete study visits every 12 weeks until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

6.13. Post Study Care

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

6.14. HIV-1 Virologic Failure

HIV-1 virologic failure is defined as confirmed virologic rebound or HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation, Week 48, or 96.

6.14.1. Management of HIV-1 Virologic Rebound

Subjects who meet the criteria listed below will be considered to have HIV-1 virologic rebound:

- At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR

- At any visit, a > 1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit

At any visit after achieving HIV-1 RNA < 50 copies/mL, if the HIV-1 RNA is ≥ 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, no further action is required. If the repeat result is ≥ 50 copies/mL subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA virologic rebound) for confirmation of virologic rebound. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the blood sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing.

All subjects with post-baseline resistance analyses will also be analyzed for their HIV-1 RT, PR, and IN genotypes and phenotypes from stored baseline samples. After a subject's first post-baseline resistance test, additional testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion or per local treatment guidelines.

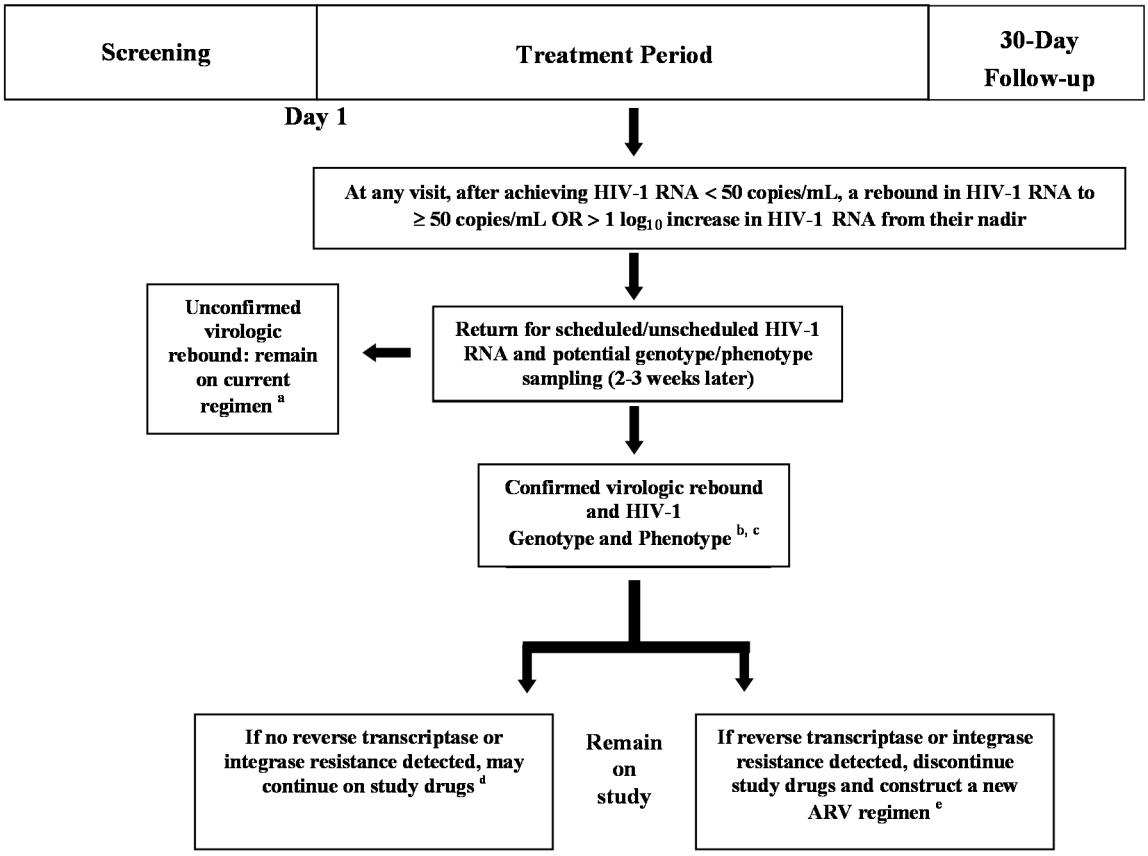
If no HIV-1 resistance is detected from the genotype or phenotype, the subject may remain on study drugs and a repeat HIV-1 RNA should be performed (2 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug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

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

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

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

Figure 6-1. Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject will remain on their current regimen.
b If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase) will be analyzed.
c Based on the results of the genotypic and phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping or phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator.
d If no resistance is detected, HIV-1 RNA will be repeated (2-3 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with the Medical Monitor prior to study drug discontinuation
e A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

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

Subjects with HIV-1 RNA ≥ 50 copies/mL at study discontinuation (at or after Week 8) or last visit will be considered virologic failures. However, if the HIV-1 RNA is ≥ 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, the subject will not be considered a virologic failure.

Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 and/or Week 96 will be asked to return for an unscheduled visit within the visit window for a retest. If the HIV-1 RNA is ≥ 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, the subject will not be considered a virologic failure and no further action is needed.

Subjects with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit, Week 48, and/or Week 96 will also have resistance testing conducted.

6.15. HBV Resistance Surveillance

Sequencing analysis of the HBV pol/RT will be attempted for all subjects who remain viremic (HBV DNA ≥ 69 IU/mL) at Weeks 48 and 96 (or Early Study Drug Discontinuation Visit as early as Week 8), and for those with virologic breakthrough defined as:

- Two consecutive HBV DNA values ≥ 69 IU/mL after achieving < 69 IU/mL, or
- Two consecutive ≥ 1.0 Log_{10} increases in HBV DNA from nadir for those who did not achieve a result < 69 IU/mL

Sequencing of the corresponding Day 1 sample will also be conducted for any subject who remains viremic or experiences virologic breakthrough. As it may not be known at the time of the visit whether a patient is viremic or if it will be their last study visit, a separate virology sample for potential resistance surveillance will be collected at each study visit. Phenotypic analysis will be performed for adherent subjects that are subjected to sequence analysis.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

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

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

Serious Adverse Events

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead 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 reporting form and submit within 24 hours 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.

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

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

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

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

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

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

7.5. Toxicity Management

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

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

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

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

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

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

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

In On-Treatment ALT Flare is defined as:

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

7.5.4.1. Management of ALT Flare in Subjects Receiving Study Medication

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

- Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.
- If the ALT elevation is confirmed, request the central clinical laboratory to conduct reflex testing for 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 subject may remain on study medication and should be monitored weekly as long as ALT levels return to normal or Day 1 level. During monitoring, if the ALT values remain persistently elevated, the Investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

Elevated Liver Enzymes, Elevated Liver Function Tests

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

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

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

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

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

7.5.5. Management of Potential Nephrotoxicity

Estimated glomerular filtration rate (eGFR), according to the Cockcroft-Gault formula for creatinine clearance, will be followed post-baseline during the study. All subjects 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 subjects 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 drugs.

For subjects 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.

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

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

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 subject 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 subject to continue on treatment with standard follow-up visits as described in the protocol.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

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

Refer to 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 Sections 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. 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 Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

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

Special situations involving non-Gilead concomitant medications 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 7.6.1 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the efficacy of FDC B/F/TAF versus a regimen of DTG + F/TDF in HIV-1 and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

- To evaluate the efficacy of FDC B/F/TAF versus a regimen of DTG + F/TDF in HIV-1 and HBV treatment naïve, HIV-1 and HBV co-infected subjects as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48

The secondary objectives of this study are:

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 96

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96

- To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with ALT normalization at Weeks 48 and 96

- To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of subjects with HBsAg loss at Weeks 48 and 96

- To evaluate the safety and tolerability of the two treatment groups through Week 96

8.1.2. Primary Endpoints

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

The co-primary efficacy endpoint is the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 as defined by Missing = Failure approach.

8.1.3. Secondary Endpoint

The secondary efficacy endpoints are

- The proportion of subjects that have HIV-1 RNA < 50 copies/mL at Week 96 as defined by the US FDA-defined snapshot algorithm.
- The change from baseline in CD4 and at Weeks 48 and 96.
- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 96.
- The proportion of subjects with ALT normalization at Weeks 48 and 96.
- The proportion of subjects with HBsAg loss at Weeks 48 and 96

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

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

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set (FAS)

The primary analysis set for efficacy analyses is defined as full analysis set (FAS), which will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have at least 1 post baseline HIV-1 RNA or HBV DNA results while on study drug. Subjects will be grouped according to the treatment to which they were randomized.

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

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

Subjects meeting any of the following criteria will be excluded from the Week 48 PP analysis set for anti-HIV efficacy analysis:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 48 analysis window, except when missing due to discontinuation of study drug for lack of efficacy.
- Subjects who do not meet the inclusion criterion that the screening genotype report must show sensitivity to FTC and TFV.

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 4.3 including drugs not to be used with bictegravir, FTC, DTG, TAF, and TDF.
- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 48 Visit below the 2.5th percentile

8.2.1.2.3. Per-Protocol (PP) Analysis Set for anti-HBV Efficacy Analysis

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

Subjects meeting any of the following criteria will be excluded from the Week 48 PP analysis set for anti-HBV efficacy analysis:

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

8.2.1.3. Safety

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

8.3. 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. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purposes. Logarithm (base 10) transformation will be applied to HIV-1 RNA and HBV DNA data for efficacy analysis.

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

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

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

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

8.5. Efficacy Analysis

8.5.1. Primary Analysis

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

The co-primary efficacy endpoint is the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 as determined by Missing=Failure approach. The primary analysis of this efficacy endpoint will be based on the FAS.

8.5.1.1. The US FDA-defined Snapshot Algorithm for HIV-1

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

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

- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects

  a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or

  b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and

     i) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or

     ii) Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than adverse event (AE), death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

- **No Virologic Data in the Week 48 analysis window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:

  a) Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death (regardless of whether the last available on-treatment HIV-1 RNA < 50 copies/mL or not) or,

  b) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,

  c) Missing data during the window but on study drug.

8.5.1.2. Analysis of Primary Efficacy Endpoint

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

Non-inferiority will be assessed using the conventional confidence interval approach. The point estimate of treatment difference (B/F/TAF – DTG+F/TDF) and the associated 2-sided 95% confidence interval will be constructed using a normal approximation method based on stratified Mantel-Haenszel proportions, where stratification factor include baseline HIV-1 RNA (≤ 100,000 copies/mL vs. > 100,000 copies/mL).

It will be concluded that B/F/TAF is non-inferior to DTG + F/TDF if the lower bound of the 2-sided 95% CI of the difference (B/F/TAF – DTG+F/TDF) in the response rate is greater than -12%.

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

8.5.1.3. Analysis of Co-Primary Efficacy Endpoint for HBV

The null hypothesis is that the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 as determined by Missing=Failure approach in B/F/TAF is at least 12% lower than the response rate in DTG + F/TDF; the alternative hypothesis is that the response rate in B/F/TAF is less than 12% lower than that in DTG + F/TDF. For Missing = Failure approach, all missing data will be treated as HBV DNA ≥ 29 IU/mL.

Non-inferiority will be assessed similarly as for the primary efficacy endpoint, except the stratification factors include HBeAg status (positive vs. negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL). To control type I error for the assessment of the primary and the co-primary efficacy endpoints, the hypothesis testing will be performed using the fallback procedure {Wiens 2005} in the sequential order with pre-specified 1-sided alpha level. The primary hypothesis of non-inferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the FDA snapshot analysis) will be tested first. Non-inferiority test will be performed at one-sided, 0.025 alpha level. If non-inferiority is established, the co-primary hypothesis of non-inferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 will be tested second at one-sided, 0.025 alpha level. Otherwise, the co-primary endpoint will not be tested at all.

8.5.2. Secondary Analyses

8.5.2.1. Secondary anti-HIV Efficacy Analysis

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

The changes from baseline in CD4 cell count and CD4% at Weeks 48 and 96 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in CD4 cell count and CD4% between 2 treatment groups and the associated 95% confidence intervals will be constructed using ANOVA models, including treatment (B/F/TAF vs. DTG + F/TDF) and baseline HIV-1 RNA (≤ 100,000 copies/mL vs. > 100,000 copies/mL) as fixed effects in the model.

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

8.5.2.2. Secondary anti-HBV Efficacy Analysis

The secondary anti-HBV efficacy endpoints include: (1) the proportion of subjects with HBV DNA < 29 copies/mL at Week 96, (2) the proportion of subjects with ALT normalization (i.e., subjects had ALT > ULN at baseline and a ALT ≤ ULN at the given post-baseline) at Weeks 48 and 96, and (3) the proportion of subjects with HBsAg loss at Weeks 48 and 96.

All these three anti-HBV efficacy endpoints will be analyzed using both Missing = Failure and Missing = Excluded approach. The 95% CIs will be constructed in the similar manner as described for the primary efficacy endpoint with stratification factors of HBeAg status (positive vs. negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs. ≥ 8 $\log_{10}$ IU/mL).

8.6. Safety Analysis

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

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

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

8.6.1. Extent of Exposure

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

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

Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

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

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

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

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

A listing of Stage 3 Opportunistic Illnesses in HIV can be found in Appendix 7

8.6.3. Laboratory Evaluations

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

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

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment. If baseline data are missing, then any graded abnormality (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 drug or after the last dose of study drug plus 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs will be summarized as appropriate.

8.7. Pharmacokinetic Analysis

Pharmacokinetic concentration data will be listed.

8.8. Sample Size

A total of approximately 240 HIV-1 and HBV co-infected subjects, randomized in a 1:1 ratio to 2 treatment groups (120 subjects per treatment group), achieves 90% power to detect a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA-defined snapshot algorithm) difference between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have a response rate of 91% (based on Gilead Studies GS-US-380-1489 and GS-US-380-1490), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

A total of approximately 240 subjects also provides 81% power to detect a non-inferiority margin of 12% with respect to the co-primary efficacy endpoint of the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. It was assumed that both treatment groups have a response rate of 88% (based on Gilead Studies GS-US-320-0108 and GS-US-320-0110, with an assumption that 80% enrolled subjects were HBeAg negative and 20% were HBeAg positive), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

8.9. Data Monitoring Committee

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

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

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

8.10. Analysis Schedule

The Weeks 48 and 96 analyses will be conducted after all subjects either complete their Week 48 and 96 visits or prematurely discontinue from the study drug, respectively. The final analysis will be performed after all subjects complete the study or prematurely discontinue from the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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

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

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

9.1.3. Informed Consent

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

investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal

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

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, IRBs/IECs and/or regulatory/health authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

Charpentier C, Le MP, Joly V, Visseaux B, Lariven S, Phung B, et al. Use of PCR Signal and Therapeutic Drug Monitoring in a Switch Cohort Study to Tenofovir/Emtricitabine/Rilpivirine: A W96 Follow-Up. PLoS ONE 2015;10 (7):e0134430.

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

Drake A, Nijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. Clin Infect Dis 2004;39 (1):129-32.

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.

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

Gorden DL, Fingleton B, Crawford HC, Jansen DE, Lepage M, Matrisian LM. Resident stromal cell-derived MMP-9 promotes the growth of colorectal metastases in the liver microenvironment. Int J Cancer 2007;121 (3):495-500.

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.

Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, Francis IR, et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. J Infect Dis 2003;187 (12):1924-33.

Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. N Engl J Med 2012;366 (19):1749-52.

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.

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

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

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.

Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of hypotheses. J Biopharm Stat 2005;15 (6):929-42.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Fixed Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment Naïve, HIV-1 and Hepatitis B Co-Infected Adults

GS-US-380-4458 Amendment 2, 06 July 2018

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

PPD

PPD (Printed)

PPD

Signature

06 July 2018

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table (Blinded Phase)

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, q]										Post-Week 96[e, r]	End of Blinded Treatment Visit	30-Day Follow-up[p]	Early Study Drugs DC[c]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Informed Consent	X															
Medical History	X															
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Complete/Symptom-Directed Physical Exam	**X**	**X**	X[d]	X[d]	X[d]	**X**	X[d]	**X**	X[d]	X[d]	X[d]	**X**	X[d]	**X**	X[d,f]	**X[f]**
12-Lead ECG (performed supine)	X															
Height	X															
Vital signs (blood pressure, pulse, respiration rate, and temperature), and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Urine Sample for Markers of Renal Dysfunction		X				X		X				X				X
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[i]		X				X		X		X		X	X[i]	X		

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, q]										Post-Week 96[e, r]	End of Blinded Treatment Visit	30-Day Follow-up[p]	Early Study Drugs DC[c]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X
Hematology Profile[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and CD4%	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X	X	X
Blood Storage Samples[o]		X	X	X	X	X	X	X	X	X	X	X	X	X		X
HCV Serology[u]	X							X				X	X			
HIV-1 Genotype[k]	X															
HIV-1 Genotype/Phenotype[e]								X[e]				X[e]				X[e]
HBV Blood panel[t]	X	X			X	X	X	X	X	X	X	X	X[t]			
HBV Genotyping (A-H)		X														
Plasma HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum sample HBV Resistance Surveillance[w]		X	X	X	X	X	X	X[w]	X	X	X	X	X[w]	X	X	X[w]
Trough PK Blood Sample[l]			X		X		X									
Post-Dose PK Blood Sample[m]				X		X										

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, q]										Post-Week 96[e, r]	End of Blinded Treatment Visit	30-Day Follow-up[p]	Early Study Drugs DC[c]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
CCI																
Randomization[v]		X														
Provide subject dosing diary to subjects		X	X	X	X	X										
Study Drug Dispensation		X[b]	X	X	X	X	X	X	X	X	X	X	X	X[s]		
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X		X

a. Evaluations to be completed within 30 days prior to Day 1.
b. Administration of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit.
c. Early Study Drugs Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit even if the subject discontinues study drug during the blinded phase.
d. Symptom-directed physical examination as needed. After Week 96 visit, complete physical exam to be completed every 48 weeks.
e. HIV-1 genotype and phenotype of protease, reverse transcriptase, and integrase testing will be completed for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.14). Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 and 96 will be asked to return for an unscheduled visit within the visit window for a retest. Subjects with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit, Week 48 or 96 will also have resistance testing conducted.
f. Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
g. Females of childbearing potential only. Serum pregnancy testing will be performed at the Screening visit. Urine pregnancy testing will be performed at Day 1 and all subsequent study visits (except the 30 Day-Follow-up Visit). Positive urine pregnancy tests will be confirmed with a serum test.
h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At Day 1, Weeks 24, 48, 72, 96, every 24 weeks post Week 96, and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments every 24 weeks and not as part of the chemistry profile. PT/INR will be performed at Screening and Day 1.

i. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. After Week 96 Visit, metabolic assessments will be completed every 24 weeks.
j. Complete blood count with differential and platelet count.
k. The Investigator must have received the results from the screening HIV-1 genotype report before proceeding with the Day 1 visit. Screening HIV-1 genotype report must show sensitivity to TFV and FTC. If genotype results from a local laboratory obtained ≤ 90 days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed.
l. Trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4, 12 and 36.
m. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose at Weeks 8 and 24.
n. CD4+ cell count and CD4% to be completed at all study visits.
o. Plasma and serum blood storage samples will be collected for safety, virology or PK testing. Whole blood storage samples will be collected for safety, virology or PK testing at Day 1, Week 48 and Week 96 visits.
p. Only required for those subjects who complete an End of Blinded Treatment Visit and do not wish to enroll in the open-label rollover extension or those subjects who prematurely discontinue study drugs prior to the End of Blinded Treatment Visit and do not continue in the study through at least one subsequent visit after the Early Study Drugs Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
q. Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days through to Week 96, unless otherwise specified. The visit window at Weeks 48 and 96 will be ± 6 weeks of the protocol-specified visit date.
r. After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Visit window of ± 6 days for study visits post Week 96.
s. Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension.
t. HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab). After Week 96, HBV serology will be performed every 24 weeks.
u. Hepatitis C virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed. After Week 96 visit, testing to be performed every 48 weeks
v. Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.
w. Genotypic analysis of HBV polymerase/reverse transcriptase (pol/RT) for resistance surveillance will be attempted for all subjects who remain viremic (HBV ≥ 69 IU/mL) at Week 48 and 96 (or early study drug discontinuation visit as early as Week 8) and for those with virologic breakthrough as defined in Section 6.15.

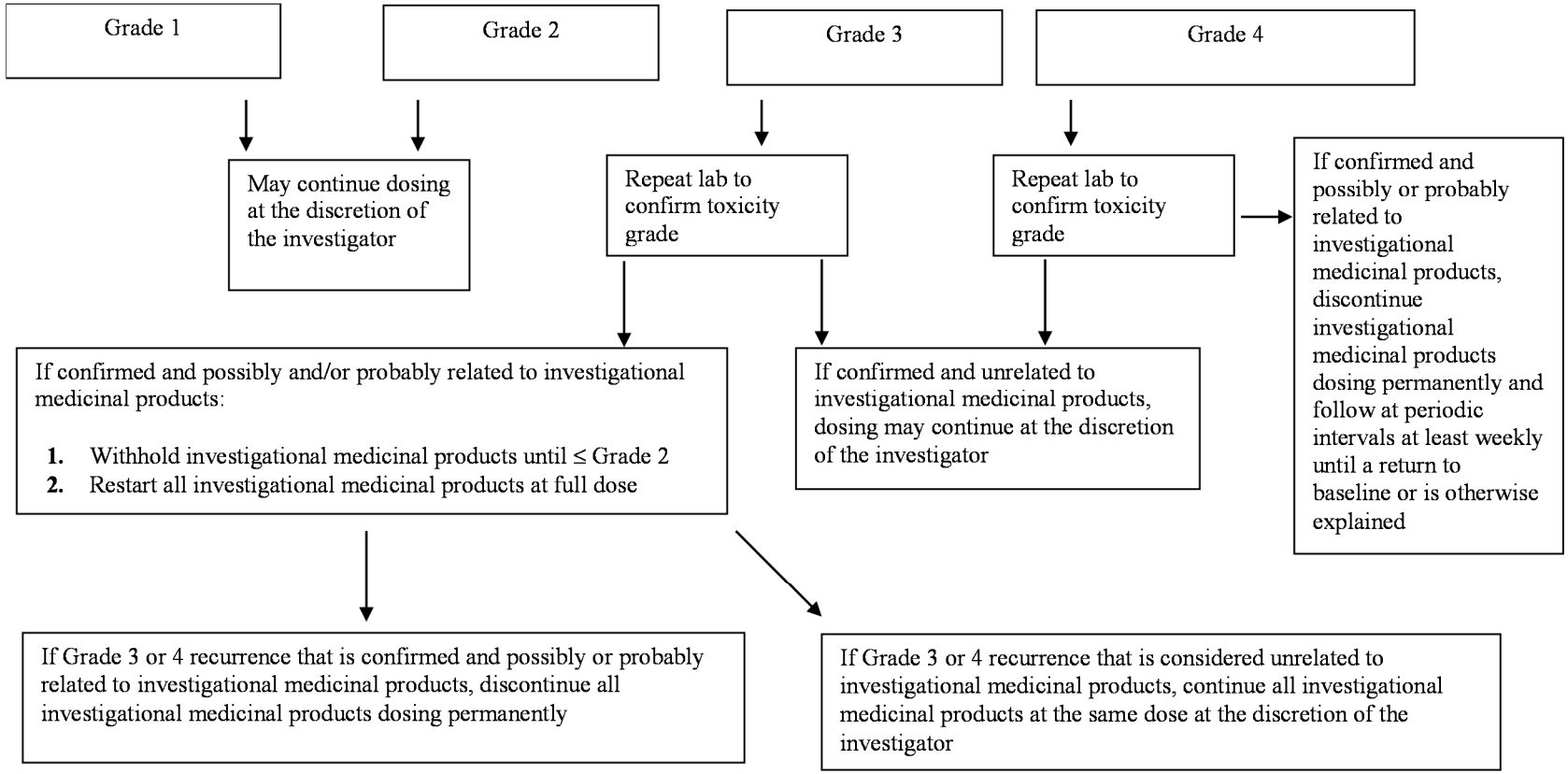
Appendix 3. Study Procedures Table (Open Label Rollover Extension)

Study Procedures	Post End of Blinded Treatment Visit (every 12 weeks)[a,e,l]	30-Day Follow-up[k]	Early Study Drugs DC[c]
Adverse Events	X	X[f]	X[f]
Concomitant Medications	X	X	X
Complete/Symptom-Directed Physical Exam	X[d]	X[d,f]	**X**[f]
Vital signs (blood pressure, pulse, respiration rate, and temperature) and Weight	X	X	X
Urinalysis	X	X[f]	X[f]
Urine Pregnancy Test[g]	X		X
Chemistry Profile[h]	X	X[f]	X[f]
Metabolic Assessments[i]	X		
Estimated Glomerular Filtration Rate	X	X[f]	X
Hematology Profile[j]	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X
CD4+ Cell Count and CD4%	X	X	X
Blood Storage Sample[o]	X		X
HBV Blood Panel[m]	X [m]		
Plasma HBV DNA	X		
HCV Serology[n]	X[n]		
HIV-1 Genotype/Phenotype[e]			X[e]
Study Drug Dispensation[b]	X		
Study Drug Accountability	X		X

a. Once the last subject completes the Week 96 visit and Gilead completes the Week 96 analysis, all subjects will return to the clinic (within 30 days ± 6 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected subjects following review of unblinded data, subjects in a country where B/F/TAF FDC is not available, will be given the option to receive B/F/TAF FDC in an open label extension phase until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

b. Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension.
c. Subjects who discontinue study drug during the open label rollover extension portion of the study will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drugs Discontinuation Visit followed by a 30-Day Follow-Up Visit. The subject will not continue attending the scheduled study visits.
d. Symptom-directed physical examination as needed.
e. HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.14).
f. Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to Day 1, or is otherwise explained.
g. Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h. Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At End of Blinded Treatment Visit and every 24 weeks after the End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
i. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) every 24 weeks. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j. Complete blood count with differential and platelet count.
k. Subjects who complete the open-label rollover extension will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit. Subjects who permanently discontinue study drugs during the open-label rollover extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
l. Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the End of Blinded Treatment Visit date through Week 12 OL and completed within ± 6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified
m. HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab will be performed every 48 weeks..
n. Hepatitis C virus (HCVAb) serology will be performed every 48 weeks. Subjects who are HCVAb positive will have a HCV RNA test performed.
o. Plasma and serum blood storage samples will be collected for safety, virology or PK testing..

Appendix 4. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	>130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	>3.37 to 4.92 mmol/L	>4.92 mmol/L	
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 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 subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

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

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

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
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
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle 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 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

The data on B/F/TAF in pregnant women is limited. 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 bictegravir 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 versions of the B/F/TAF investigator's brochure and F/TDF and DTG prescribing labels for additional information.

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 Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the 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 women of childbearing potential with infrequent or irregular periods. Female subjects 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 subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 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)

Female subjects who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Female subjects 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

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

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant, 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. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects who become pregnant will be discontinued from the study and their study treatment assignment will be unblinded by the Investigator and provided to the subject.

Subjects 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 7.6.2.1.

Appendix 7. 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}