CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b, Open-label study to Evaluate the PK, Safety and Efficacy of B/F/TAF in HIV-1 infected, Virologically Suppressed, Pregnant Women in their Second and Third Trimesters	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	125589	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	Not Available	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-380-5310	
Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original:	02 Apr 2019

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

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 1b, Open-label study to Evaluate the PK, Safety and Efficacy of B/F/TAF in HIV-1 infected, Virologically Suppressed, Pregnant Women in their Second and Third Trimesters
IND Number:	125589
EudraCT Number:	Not applicable
Clinical Trials.gov Identifier:	Not available
Study Centers Planned:	Approximately 20 centers globally
Objectives:	**The primary objective of this study is as follows:** • To evaluate the steady state pharmacokinetics (PK) of bictegravir (BIC) and confirm the dose of BIC/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg fixed dose combination (FDC) in the second and third trimesters of pregnancy **The secondary objectives of this study are as follows:** • To evaluate the steady state PK of emtricitabine (FTC) and TAF in the second and third trimesters of pregnancy • To evaluate maintenance of HIV-1 virologic suppression in pregnant women receiving the B/F/TAF FDC during the second and/or third trimesters **The exploratory objectives of this study are as follows:** • To assess frequency of HIV-1 transmission from pregnant women taking B/F/TAF during the second and third trimesters to the neonate • To evaluate the safety and tolerability of the B/F/TAF FDC in HIV-1 infected virologically suppressed pregnant women during the second and third trimesters through post-partum • To evaluate the safety of B/F/TAF in neonates with in utero exposure to B/F/TAF

	• To explore the PK of tenofovir diphosphate (TFV-DP) in PBMCs in pregnancy following administration of the B/F/TAF FDC • To explore the elimination of BIC and TAF in neonates from in utero exposure • To explore placental transfer of BIC and TAF
Study Design:	Phase 1b, open-label, multiple dose study in HIV-1 infected pregnant women in their second and/or third trimesters
Number of Participants Planned:	Up to 35 participants total. At least 25 participants will be enrolled to obtain at least 20 evaluable pairs of PK assessments between the second trimester and post-partum and at least 20 evaluable pairs of PK assessment between the third trimester and post-partum. Replacement participants may be enrolled if originally enrolled participants do not complete all intensive PK visits as expected. Infants born to women participating in the study will be followed from birth to 4-8 weeks of age if consent is obtained from the parents/legal guardian.
Target Population:	HIV-1 infected pregnant female participants who are virologically suppressed for ≥ 6 months prior to screening and are at least 12 weeks gestation but less than 31 weeks gestation at the time of the Screening Visit. Infants born to women participating in the study will be followed from birth to 4-8 weeks of age if consent is obtained from the parents/legal guardian.
Duration of Treatment:	Participants will be treated for up to approximately 38 weeks (from the second or third trimesters of pregnancy, depending on enrollment, through 12 weeks post-partum). Participants who complete the study through Week 12 post-partum visit will be required to return to the clinic 30 days after the Week 12 post-partum visit for a 30-Day Follow-Up Visit.
Diagnosis and Main Eligibility Criteria:	HIV-1 infected women with singleton pregnancy and meet the following criteria at screening: • At least 12 weeks but not more than 31 weeks pregnant • Documented plasma HIV-1 RNA < 50 copies/mL on a stable regimen (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL) for ≥ 6 months preceding the Screening visit

- The last two HIV-1 RNA measurements prior to screening must be < 50 copies/mL; however, unconfirmed virologic elevations of ≥ 50 copies/mL; (transient detectable viremia, or "blip") in the past are acceptable.
- Estimated GFR (calculated by Cockcroft-Gault) ≥ 90 mL/min
- No documented or suspected resistance to FTC, TFV, or INSTIs including, but not limited to, the reverse transcriptase resistance mutations K65R or M184V/I
- No chronic hepatitis B virus (HBV) infection
- Agree not to breastfeed for the duration of the study
- Normal ultrasound with no evidence of any fetal malformation or structural abnormality affecting either fetus or placenta
- Normal maternal alfa-fetoprotein level

Study Procedures/ Frequency:

MATERNAL

Following completion of Screening and Day 1 visits, eligible participants will be required to return for study visits at Weeks 4, 8, 12, 16, 20 and 24 dependent on time of enrollment (unless delivery has occurred by that time point). The day of delivery will be considered as the Delivery Visit for study purposes.

Following delivery, participants will be required to return for study visits for Weeks 6 and 12 post-partum visits and a 30-Day Follow-up Visit.

For all eligible participants, blood samples will be collected at Day 1 and all subsequent visits.

For all eligible participants, urine samples will be collected at Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits.

Assessments of adverse events and concomitant medications are performed at each visit.

Pharmacokinetic Assessments

- **Study Drug Administration for Intensive Pharmacokinetic**

  On the days of intensive pharmacokinetic (iPK) sampling, study drug will be administered in the morning in the clinic. Following study drug administration participants will fast until after collection of the 2 hour PK sample. Additionally, participants will be restricted from water consumption 1 hour before and 1 hour after study drug administration (except for the 240 mL given with the study drug).

If a subject is unable to fast for the iPK visit, the visit may proceed. Participants should be consistent if they choose to fast or not fast during the iPK visits (i.e. if the participant fasts at the first iPK visit, then they should fast at all other iPK visits). Diary cards will be provided to all participants to record the time of study drug administration prior to the iPK visit.

- **PK Collection During Pregnancy**:

  Intensive PK visits will be completed after subject administers B/F/TAF for at least 3 weeks.

  For participants who enroll during the second trimester, serial blood samples for iPK evaluation will be collected at or between 20 to 28 weeks of gestation, and during the third trimester, at or between 30 to 38 weeks of gestation.

  For participants who enroll during the third trimester, serial blood samples for iPK evaluation will be collected at or between 30 to 38 weeks of gestation.

- **PK Collection Post-partum**:

  Serial blood samples for iPK evaluation will be collected for all participants at Week 6 and Week 12 post-partum visits.

- **Intensive PK Sample Collection Timepoints:**

  Blood samples will be collected at the following time points at the iPK visits:

  — Pre-dose (≤ 5 minutes prior to dosing)

  — 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose

  A single anytime PK sample will be collected at the Early Study Drug Discontinuation (ESDD) Visit, if applicable

- **PBMC Collection**:

  For participants enrolled at sites that can process PBMC samples, a trough PBMC sample will be collected 24 hours following the in-clinic dose administered at the iPK visits.

- **Sparse PK Collection at the Delivery Visit**: A single maternal blood sample and an umbilical cord blood sample after cord clamping will be collected soon after delivery.

Safety Assessments

- Complete physical exam: Screening, Day 1, Week 4, Week 12, Weeks 6 and 12 post-partum, and at the ESDD Visit, if applicable.
- Symptom-driven physical exam: Weeks 8, 16, 20 and 24, and 30-Day Follow-up Visit
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Day 1 and all subsequent visits
- Height: Screening
- Weight: Screening, Day 1 and all subsequent visits
- Estimated glomerular filtration rate according to the Cockcroft-Gault formula: Screening, Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits
- Clinical laboratory tests (hematology, chemistry, and urinalysis): Screening, Day 1, Weeks 12 and 24, Weeks 6 and 12 post-partum, 30-Day Follow-up Visit and at the ESDD visit, if applicable
- Maternal alfa-fetoprotein level: Screening
- Urine drug and alcohol assessments: Screening, Day 1
- 12-lead electrocardiogram (ECG): Screening
- Hepatitis B virus, hepatitis C virus testing: Screening
- HIV-1 RNA testing: Screening, Day 1 and all subsequent visits
- CD4+ cell count: Screening, Day 1, and Week 12 post-partum visit.

Assessments at the Delivery Visit

At the Delivery Visit, the date of delivery and outcome of the pregnancy will be recorded and a blood sample will be collected for HIV-1 RNA testing. Additionally, blood samples will be collected for PK assessments as described above.

Assessment of adverse events (AEs) and concomitant medications will continue throughout the study. All clinical and clinically significant laboratory toxicities will be managed per protocol requirements.

INFANTS

Infants will be enrolled and followed from birth to 4 to 8 weeks of age if parent/legal guardian consent is provided.

	Sparse PK Collection: Sparse PK blood samples will be collected, if possible, at the following time points: at or between 0 to < 2 hours, 2 to < 3 hours, 3 to 8 hours, 18 to 28 hours, 36 to 72 hours, and 5 to 7 days after birth. These time points may vary based on birth weight, additional instructions will be included in the Pharmacokinetic Sample Collection and Processing Instructions Manual. **Neonatal Assessments** • Complete physical exam: Physical examination at birth and once between 4 to 8 weeks of age • Vital signs (heart rate, respiration rate, and body temperature): at birth and once between 4 to 8 weeks of age • Apgar scoring: at 5 and 10 minutes after delivery, if recorded • Anthropometric measures: Head circumference, weight and length at birth and once between 4 to 8 weeks of age • Blood samples will be collected for PK assessments • HIV-1 RNA and safety assessments which includes CBC, LFTs (ALT, AST, total and direct bilirubin) may be completed using the sparse PK samples collected on the day of birth, if there is sufficient volume. If blood volume is insufficient, results from testing performed per standard of care will be obtained. • HIV-1 RNA and safety assessments may be completed once between 4 to 8 weeks of age or results from testing performed per standard of care between 4 to 8 weeks of age will be obtained.
Test Product, Dose, and Mode of Administration:	FDC of bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF 50/200/25 mg) administered orally, once daily without regard to food
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Adverse events and clinical laboratory tests to evaluate the safety and tolerability of the treatment regimen.
Efficacy:	The efficacy endpoint is: Maternal HIV-1 RNA < 50 copies/mL at the time of delivery

Pharmacokinetics:	Plasma concentrations of BIC, FTC and TAF will be determined and PK evaluated, as applicable. Protein binding of BIC from maternal intensive PK samples will be assessed at 24 hours post-dose. Protein binding of TAF from maternal intensive PK samples may be assessed at 3 hours post-dose. Plasma protein binding of BIC and TAF from maternal samples may also be evaluated at an additional time point corresponding to T_{max} of the respective analyte. Plasma concentrations of other metabolites may be determined and PK explored. Intracellular concentrations of TFV-DP in PBMCs will be determined, as applicable. The following plasma PK parameters will be calculated for BIC, FTC and TAF, as applicable: AUC_{tau}, AUC_{last}, C_{max}, C_{tau}, C_{last}, T_{max}, λ_z, $CL_{/F}$, $V_{z/F}$, $T_{½}$, and cord blood to maternal plasma concentration ratios, as applicable. The PK of other analytes may be explored. Concentrations of TFV-DP in peripheral blood mononuclear cells (PBMCs) will be analyzed and C_{tau} will be calculated, as applicable. Additionally, BIC and TAF $T_{½}$ will be calculated in infants where possible.
Statistical Methods:	**Pharmacokinetics:** Plasma concentrations and PK parameters will be listed and summarized using descriptive statistics by visit for maternal and infant, respectively. An analysis of variance (ANOVA) using a mixed-effects model with visit as a fixed effect and subject as a random effect will be fitted to the natural logarithmic transformation of maternal PK parameters (AUC_{tau}, C_{max} and C_{tau}, as applicable) for each analyte of interest. Two-sided 90% confidence intervals (CIs) will be calculated for the ratios of geometric least-squares means (GLSMs) between pregnancy (second or third trimester) and 12 weeks post-partum. The terminal half-life of BIC for infants, and the cord blood to maternal plasma concentrations ratio for BIC at delivery will be calculated and summarized. **Efficacy:** The proportion of participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery will be summarized using the missing = excluded approach for imputing missing HIV-1 RNA values. Efficacy data for infants will be listed and may be summarized by visit if applicable.

Safety:

The AE data will be listed by subject. Treatment-emergent AEs, serious adverse events (SAEs), and AEs leading to permanent study drug discontinuation will be summarized by system organ class, and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Listings of individual subject vital signs, 12-lead ECG parameters, and laboratory results will be provided. Laboratory results and change from baseline for vital signs and selected lab tests will be summarized at scheduled visits. The incidence of treatment-emergent laboratory abnormalities will be summarized.

Safety data for infants will be listed and may be summarized if applicable.

Sample Size:

With 20 evaluable participants, the study has at least 74% power to show that the lower bound of the 90% CI of the ratio for AUC_{tau} of BIC during pregnancy relative to post-partum is > 50%, assuming a decrease of 40% in AUC_{tau} of BIC during pregnancy relative to post-partum. It was assumed that a standard deviation (SD) of BIC AUC_{tau} is no more than 0.34 on a natural logarithm scale, which is supported by a pooled PK analysis from 4 previous Gilead Phase 3 studies. With 25% overage, a total sample size of at least 25 participants will be required.

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, GS-9883
B/F/TAF	bictegravir/emtricitabine/ tenofovir alafenamide, Biktarvy®
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CHB	chronic hepatitis B
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COBI, /C	Cobicistat
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CYP	cytochrome P450
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DTG	dolutegravir, Tivicay®
ECG	Electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
FAS	full analysis set
EVG	elvitegravir, E
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, Genvoya®
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, Stribild®

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

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

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.4 million people in North America and Western and Central Europe living with HIV-1 and 37 million people worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {Mocroft 1998, Palella 1998, Sterne 2005}.

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

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

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

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

Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}. Virologically suppressive ART has also contributed to a decline in HIV incidence in communities with high rates of virologic suppression, by reducing the transmissibility of infected individuals on treatment {Grabowski 2017, Kurth 2011}.

All pregnant women living with HIV infection should receive effective antiretroviral therapy with at least three drugs for their own health and for the prevention of perinatal transmission of HIV. Treatment options for pregnant women may be limited due to risk of toxicity (e.g., didanosine, stavudine, full-dose ritonavir) or risk of low drug exposure and risk of virologic failure (e.g., elvitegravir/cobicistat) or risk of teratogenicity. Although highly effective and well tolerated treatment options are available for the treatment of HIV infection in adults, PK and safety data to inform the use of newer ARVs in pregnant women remains limited {Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 2018}.

1.2. B/F/TAF

1.2.1. General Information

Bictegravir, a potent inhibitor of HIV-1 integrase, is now approved for the treatment of HIV infection as a component of FDC of B/F/TAF. For further information on bictegavir, refer to the investigator's brochure.

1.2.2. Preclinical Pharmacology and Toxicology

A core battery of safety pharmacology studies have been conducted with bictegravir. These include assessments of cytotoxicity, off-target receptor and ion-channel binding, effects on human Ether-à-go-go-Related Gene (hERG) potassium current and papillary muscle action potential, and in vivo studies in rats and dogs that evaluated effects of bictegravir on all major organ systems. Please refer to the investigator's brochure for details.

1.2.2.1. Pharmacology

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

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

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

1.2.2.2. Toxicology

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

1.2.3. Clinical Trials of Bictegravir and B/F/TAF

Please refer to the B/F/TAF investigator's brochure for a list of clinical studies of BIC and B/F/TAF as well as further information about these studies.

1.2.3.1. Phase 1 Safety and Pharmacokinetics

Study GS-US-141-1218 was a four part, first-in-human study. Parts A and B were randomized, double-blind, placebo-controlled, single and multiple ascending dose studies of BIC in healthy male and female participants which helped establish the PK of BIC and evaluated the drug-drug interaction potential with F/TAF FDC. Please see the investigator's brochure for additional details.

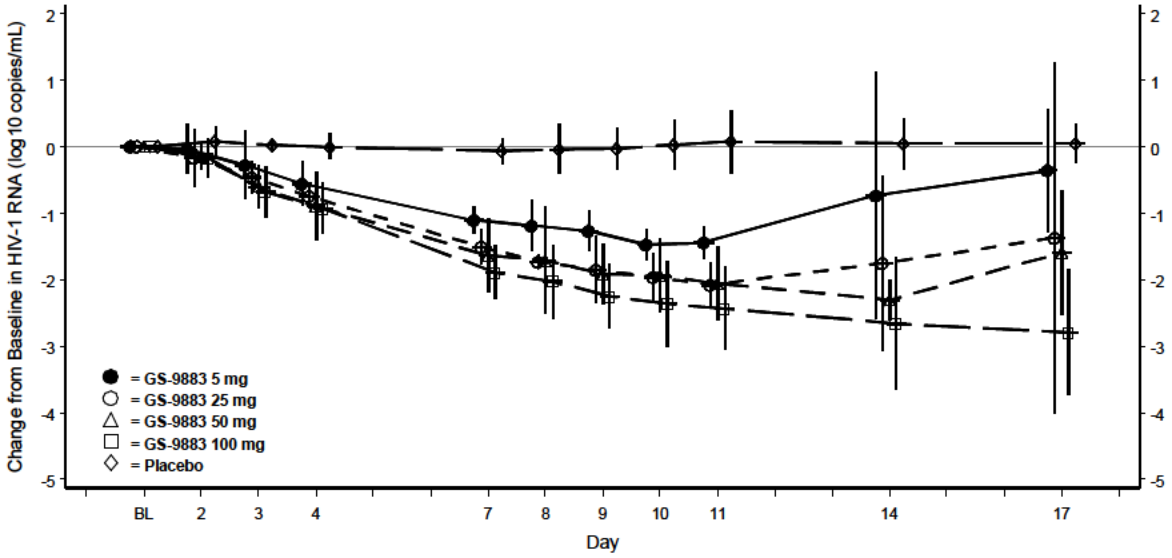
1.2.3.2. Phase 1b Proof of Concept

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

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

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

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



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

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

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

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

The primary efficacy endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm. The percentages of participants with HIV-1 RNA < 50 copies/mL at Week 24 was high in both groups, as follows: BIC+FTC/TAF 96.9%; DTG+FTC/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 (BIC+FTC/TAF - DTG+FTC/TAF) was greater than the prespecified −12% margin, BIC+FTC/TAF was determined to be noninferior to DTG+FTC/TAF.

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

1.2.3.4. Summary of Phase 3 Studies

Treatment-Naïve Patients

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

In Studies 1489 and 1490, the mean age was 35 years (range 18-77), 89% were male, 58% were White, 33% were Black, and 3% were Asian. 24% percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3-6.6). The mean baseline CD4+ cell count was 460 cells/mm^3 (range 0-1636) and 11% had CD4+ cell counts less than 200 cells/mm^3. 18% of patients had baseline viral loads greater than 100,000 copies/mL. In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies/mL to less than or equal to 400,000 copies/mL, or greater than 400,000 copies/mL), by CD4 count (less than 50 cells/µL, 50-199 cells/µL, or greater than or equal to 200 cells/µL), and by region (US or ex-US).

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

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

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

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

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

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

Bone Mineral Density:

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

Virologically Suppressed Patients

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

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

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

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

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

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

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

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

Bone Mineral Density:

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

Virologically Suppressed Female Patients

In study 1961, the efficacy and safety of switching to B/F/TAF from either a protease inhibitor or boosted elvitegravir-containing regimen (E/C/F/TAF or E/C/F/TDF) was evaluated in HIV-1 infected, virologically suppressed women (N=470). Participants were randomized (1:1) to switch to B/F/TAF (234) or stay on baseline regimen (SBR, n=236 [E/C/F/TAF n=125; E/C/F/TDF n=98; ATV+RTV+FTC/TDF n=13]). Participant median age was 39 years 37% black, 28.3% white, 21.7% Asian and CD4 count was 686 cells/µl. In Study 1961 at Week 48, switching to B/F/TAF FDC was noninferior to SBR. The percentages of patients with HIV-1 RNA ≥ 50 copies/mL and who maintained HIV-1 RNA < 50 copies/mL were similar between the B/F/TAF FDC and SBR groups. The median change from baseline in CD4+ count at Week 48 was +32 cells/mm3 in patients who switched to B/F/TAF FDC and +23 cells/mm3 in patients in the SBR group.

Treatment outcomes of Study 1961 through Week 48 are presented in Table 1-3.

Table 1-3. GS-US-380-1961: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (Full Analysis Set)

			B/F/TAF vs SBR	
	B/F/TAF (N=234)	**SBR (N=236)**	**p-value**	**Difference in Percentages (95.001% CI)**
HIV-1 RNA < 50 copies/mL	224 (95.7%)	225 (95.3%)	1.00	0.4% (-3.7% to 4.5%)
HIV-1 RNA >= 50 copies/mL	4 (1.7%)	4 (1.7%)	1.00	0.0% (-2.9% to 2.9%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	4 (1.7%)	4 (1.7%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
Discontinued Study Drug Due to Other Reasonsa and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
No Virologic Data in Week 48 Window	6 (2.6%)	7 (3.0%)		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	0	1 (0.4%)		
Discontinued Study Drug Due to Other Reasonsa and Last Available HIV-1 RNA < 50 copies/mL	3 (1.3%)	4 (1.7%)		
Missing Data During Window but on Study Drug	3 (1.3%)	2 (0.8%)		

The Week 48 window is between Days 295 and 378 (inclusive).
a Other reasons include participants who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
P-values for the superiority test comparing the percentages between treatment groups were from the Fisher exact test.
The difference in percentages between treatment groups and their 95.001% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

1.3. Rationale for This Study

All pregnant women living with HIV infection should receive effective antiretroviral therapy with at least three drugs for their own health and for the prevention of perinatal transmission of HIV. Treatment options for pregnant women may be limited due to risk of toxicity (e.g., didanosine, stavudine, full-dose ritonavir) or risk of low drug exposure and risk of virologic failure (e.g., elvitegravir/cobicistat) or risk of teratogenicity. Although highly effective and well tolerated treatment options are available for the treatment of HIV infection in adults, PK and safety data to inform the use of newer ARVs in pregnant women remain limited {Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 2018}.

The PK of many drugs, including ARVs, has been shown to be altered during pregnancy {Prezista USPI, Reyataz USPI, Edurant USPI, Tivicay USPI}{Gilbert 2015}.These changes in drug exposures have been attributed to the physiologic changes that occur during pregnancy, which include changes in plasma volume, protein binding, glomerular filtration rate and altered activity of drug metabolizing enzymes and transporters {Costantine 2014, Isoherranen 2013, Loebstein 1997}.

Bictegravir is an INSTI that is currently approved in a FDC of B/F/TAF for use once daily for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults {Biktarvy USPI}. Bictegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) and CYP3A4. Increased activities of CYP3A and UGT1A1 have been reported during pregnancy {Hebert 2008, Jeong 2009} and decreased exposures of other ARVs that are substrates of these enzymes (i.e, dolutegravir and raltegravir) have been observed (Mulligan 2018, Watts 2014). As such, there may be a possibility for reduced BIC exposures during pregnancy. No clinically relevant changes in the PK of FTC or TAF were observed in previous studies in HIV-infected pregnant women {Colbers 2013, Stek 2012}.

The primary objective of this study is to characterize the pharmacokinetics (PK) of BIC and confirm the dose of the B/F/TAF FDC in virologically suppressed, HIV-1 infected pregnant women. Thus, this study aims at comparing the PK of BIC, FTC and TAF in HIV-infected pregnant women in the second or third trimesters of pregnancy relative to post-partum. This study will also characterize placental transfer of BIC and TAF to understand drug distribution into the fetus and the elimination of BIC and TAF in neonates from in utero exposure. Pharmacokinetic and safety data from this study will guide dose selection of B/F/TAF in pregnancy.

1.4. Rationale for Dose Selection

B/F/TAF 50/200/25 mg is the approved dose for treatment of HIV-1 infection in adults (Biktarvy USPI).

The B/F/TAF Phase 3 studies support that virologic suppression and safety are maintained with mean BIC exposures at ~50% to 200% of the mean in adults {Lutz 2018}. Briefly, no exposure-safety relationship was observed for BIC in Phase 3, supporting the safety of increases in BIC exposures ~200% of the mean in adults. With respect to efficacy, the results of B/F/TAF Phase 3 exposure-efficacy analyses showed uniformly high virologic response rates (≥ 98.0%) across BIC exposure quartiles, with similar virologic response rates in the highest quartile and the lowest quartile observed. In the Phase 3 studies, the mean protein adjusted inhibitory quotient (IQ; C_{tau}/$paEC_{95}$ [162 ng/mL]) was 16.1.

An evaluation of individual participants' BIC IQ values as a function of whether or not the primary efficacy endpoint was met (HIV-1 RNA < 50 copies/mL at Week 48) revealed that all 27 participants who had IQ values at or below 50% of the Phase 3 mean IQ of 16.1 had HIV-1 RNA < 50 copies/mL at the Week 48 visit. Therefore, the lower boundary of the BIC therapeutic window is unknown and the 50% lower limit is conservative. Importantly, the subject with the lowest observed BIC exposure (IQ = 4.7) would maintain C_{tau} well above $paEC_{95}$ even

if their exposure decreased by 50% (IQ = 2.4). As such, participants with a decrease in exposures of 50% of the Phase 3 mean are expected to maintain virologic suppression.

The Phase 3 data support the safety of increases in BIC exposures ~200% of the mean in adults. No exposure-safety relationship was observed for BIC in Phase 3 and the highest observed individual BIC AUC_{tau} in the Phase 3 studies was approximately 230% that of the mean Phase 3 BIC AUC_{tau}, indicating that all participants with exposures around 200% of the Phase 3 mean are expected to maintain safety.

Changes in BIC exposure during the second and third trimesters of pregnancy in this study are expected to be within the range of those observed for other INSTIs that are substrates of CYP3A and UGT1A1, dolutegravir and raltegravir {Mulligan 2018, Watts 2014}. Exposures of these agents decreased 20 to 50% during pregnancy compared to post-partum. As BIC exposures ≥ 50% of the mean in adults are expected to maintain virologic suppression and no clinically relevant changes in FTC and TAF are expected, B/F/TAF is anticipated to be efficacious and well tolerated during pregnancy.

1.5. Risk/Benefit Assessment for the Study

Maintenance of virologic suppression is of paramount importance to protect the health of pregnant women and to prevent vertical transmission to the infant. In general, pregnant women are encouraged to continue their current ART regimen during pregnancy, assuming that it is effective and well-tolerated {Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 2018}. However, newer, highly effective ARVs such as B/F/TAF may provide benefits by reducing pill burden and toxicity while maintaining highly efficacious therapy without risk of drug resistance. Bictegravir did not show any risk for embryo-fetal toxicity in pre-clinical species. There is limited information on TAF in pregnancy, but TDF, a different tenofovir prodrug, is recommended in pregnancy. 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 risks of switching ARVs during pregnancy could be loss of virologic control, development of drug resistance to some of the medications in B/F/TAF or new side effects. Potential benefits may include provision of a new ARV therapy to this 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 addition, INSTIs exhibit rapid reduction of HIV-1 viral load, thereby providing a benefit to pregnant women with untreated HIV-1 infection.

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

- No clinically relevant changes in the PK of FTC or TAF were observed in previous studies in HIV-infected pregnant women
- Changes in BIC exposure during the second and third trimesters of pregnancy are anticipated to remain within the safe and efficacious ranges observed during the Phase 3 trials

- B/F/TAF has been proven to be safe, well tolerated and effective in the treatment of HIV-infected patients, including in 470 women in Study GS-US-380-1961

- No treatment emergent resistance developed in any patient treated with B/F/TAF during the Phase 2 and Phase 3 studies

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

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the steady state pharmacokinetics (PK) of bictegravir (BIC) and confirm the dose of BIC/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg fixed dose combination (FDC) in the second and third trimesters of pregnancy

The secondary objectives of this study are:

- To evaluate the steady state PK of emtricitabine (FTC) and TAF in the second and third trimesters of pregnancy
- To evaluate maintenance of HIV-1 virologic suppression in pregnant women receiving the B/F/TAF FDC during the second and/or third trimesters

The exploratory objectives of this study are as follows:

- To assess frequency of HIV-1 transmission from pregnant women taking B/F/TAF during the second and third trimesters to the neonate
- To evaluate the safety and tolerability of the B/F/TAF FDC in HIV-1 infected virologically suppressed pregnant women during the second and third trimesters through post-partum
- To evaluate the safety of B/F/TAF in neonates with in utero exposure to B/F/TAF
- To explore the PK of tenofovir diphosphate (TFV-DP) in PBMCs in pregnancy following administration of the B/F/TAF FDC
- To explore the elimination of BIC and TAF in neonates from in utero exposure
- To explore placental transfer of BIC and TAF

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The PK parameter AUC_{tau} of BIC during the second and/or third trimesters through post-partum

The secondary endpoints of this study are:

- The PK parameter AUC_{tau} for FTC and TAF, and PK parameters AUC_{last}, C_{max}, C_{tau}, C_{last}, T_{max}, $T_{1/2}$, CL/F, V_z/F, and λ_z for BIC, FTC, and TAF, as applicable

- The proportion of participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery by missing = excluded approach.

3.2. Study Design

This protocol describes an open-label, multicenter, multiple-dose study to evaluate the PK, efficacy, safety and tolerability of B/F/TAF in virologically suppressed, HIV-1 infected pregnant women in their second and third trimesters.

3.3. Study Treatments

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

3.4. Duration of Treatment

Participants will be treated for up to approximately 38 weeks. Following completion of a 30-day screening period and a Day 1 visit, eligible participants will be required to return for study visits at Weeks 4, 8, 12, 16, 20 and 24 dependent on time of enrollment (unless delivery has occurred by that time point). The day of delivery will be considered as the Delivery Visit for study purposes.

The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.

Following delivery, participants will be required to return for study visits for Weeks 6 and 12 post-partum visits. Participants who complete the study through the Week 12 post-partum visit will be required to return to the clinic 30 days after completion of the study drug dosing for a 30-Day Follow-Up Visit.

4. SUBJECT POPULATION

4.1. Number of Participants and Subject Selection

Up to 35 participants who meet all eligibility criteria will be enrolled.

At least 25 participants will be enrolled to obtain at least 20 evaluable pairs of PK assessments between the second trimesters and post-partum and at least 20 evaluable pairs of PK assessment between the third trimesters and post-partum. Replacement participants may be enrolled if participants do not complete all intensive PK visits as expected.

Infants born to women participating in the study will be followed from birth to 4-8 weeks of age if consent is obtained from the parents/legal guardian.

4.2. Inclusion Criteria

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

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

2) Female participants of age ≥ 18 to < 40 years with singleton pregnancy, at least 12 weeks but not more than 31 weeks pregnant at the time of screening

3) Agree not to breastfeed for the duration of the study

4) Currently on a stable antiretroviral regimen for ≥ 6 months preceding the screening visit

5) Documented plasma HIV-1 RNA levels of < 50 copies/mL for ≥ 6 months preceding the screening visit and have HIV-1 RNA < 50 copies/mL at the Screening Visit

    a) In the preceding 6 months prior to screening, one episode of "blip" (HIV-1 RNA ≥ 50 copies/mL and < 400 copies/mL) is acceptable, only if HIV-1 RNA is < 50 copies/mL immediately before and after the blip

    b) To determine virologic suppression in the preceding 6 months prior to screening, the lower limit of quantification (LLOQ) by the local HIV-1 RNA assay may be used, only if its LLOQ is greater than 50 copies/mL (e.g. LLOQ of 75 copies/mL)

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

    a) Historic genotype reports will be collected if available

7) Have a normal ultrasound, completed locally prior to the Day 1 visit, with no evidence of any fetal malformation or structural abnormality affecting either fetus or placenta

8) Normal maternal alfa-fetoprotein level at the Screening Visit

9) Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min according to the Cockcroft-Gault (C-G) formula {Cockcroft 1976}:

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

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

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

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

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

13) Adequate hematologic function (absolute neutrophil count ≥ 750/mm^3 (≥ 0.75 GI/L); platelets ≥ 50,000/mm^3 (≥ 50 GI/L); hemoglobin ≥ 9.5 g/dL (≥ 95 g/L))

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

15) Participants of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix 6) during the post-partum period of the study, and for 7 days following the last dose of study drug.

4.3. Exclusion Criteria

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

1) Have chronic hepatitis B virus (HBV) as determined by either:

   a) Positive HBV surface antigen (HBsAg) at the Screening Visit

   b) Negative HBV surface antigen, negative HBV surface antibody, positive HBV core antibody and quantifiable HBV DNA (HBV DNA ≥ 20 IU/mL) at the Screening Visit

2) Have active hepatitis C virus (HCV) infection

   a) Positive anti-HCV antibody and negative HCV polymerase chain reaction (PCR) results are acceptable

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

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

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

6) Malignancy within 5 years of screening other than cutaneous Kaposi's sarcoma, completely resected non-melanoma skin cancer (basal cell carcinoma or non-invasive cutaneous squamous carcinoma), or completely resected carcinoma in-situ of the cervix (CIN 3) or anus (AIN 3). A prior malignancy treated with curative therapy and for which there has been no evidence of disease for at least five years prior to screening is allowed.

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

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

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

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

11) Active tuberculosis infection

12) Known hypersensitivity to B/F/TAF, their metabolites, or formulation excipient.

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

Drug Class	**Agents Disallowed***
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	phenobarbital, phenytoin, carbamazepine, oxcarbazepine
Antimycobacterials	rifampin, rifapentine, rifabutin
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen
Herbal/Natural Supplements	St. John's Wort

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

4.4. Enrollment Criteria for Neonates

Neonates must meet the following inclusion criterion to be eligible for participation in this study.

1) Parent/legal guardian consent obtained for neonate participation.

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

1) If the mother has discontinued study drug > 24 hours prior to delivery

2) At birth, the neonate has a medical condition that, in the opinion of the Investigator precludes them from participating

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

Participants will be assigned a screening number at the time of consent. **Day 1 visit cannot occur until the Investigator has confirmed the subject's eligibility.**

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

All eligible Participants will be provided B/F/TAF on Day 1 visit. The IWRS will assign study drug bottle numbers at each study visit.

5.2. Description and Handling of B/F/TAF

5.2.1. Formulation

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

5.2.2. Packaging and Labeling

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 B/F/TAF to be distributed to centers in the US, Dominican Republic and Thailand shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), and/or other local regulations.

5.2.3. Storage and Handling

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

To ensure the stability and proper identification, study drug should not be stored in a container other than the container in which it was supplied. Keep the bottle tightly closed to protect from moisture.

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

5.3. Dosage and Administration

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

FDC of B/F/TAF containing bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25 mg will be provided to all eligible Participants at Day 1. Study drug will be administered orally at approximately the same time each day without regard to food.

5.4. Prior and Concomitant Medications

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

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

Table 5-1. Prior and Concomitant Medications

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

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

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

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

5.5. Accountability for B/F/TAF

The Investigator is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of B/F/TAF (quantity and condition). All used and unused B/F/TAF bottles dispensed to Participants must be returned to the site.

B/F/TAF accountability records will be provided to each study site to:

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

5.5.1. Investigational Medicinal Product Return or Disposal

Return and disposal of B/F/TAF will be performed as outlined in Section 9.1.8.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment

It is the responsibility of the Investigator to ensure that participants are eligible for study prior to enrollment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Participants will be screened within approximately 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 samples for the following laboratory analyses:
  - 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 participants with total amylase > 1.5 × ULN), and TSH
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology Profile: complete blood count (CBC) with differential and platelet count

- Maternal alfa-fetoprotein
- Plasma HIV-1 RNA
- Whole blood for HIV-1 genotype (if the sample is not collected at the screening visit, it may be collected at the Day 1 visit)
- CD4+ cell count
- Hepatitis B virus (HBV) blood panel: hepatitis B virus surface antigen (HBsAg), hepatitis B virus surface antibody (HBsAb) and hepatitis B virus core antibody (HBcAb)

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

  - If positive HBsAg, reflex testing for plasma HBV DNA, HBeAg (if negative, reflex HBeAb), and quantitative HBsAg
  - If positive HBcAb with negative HBsAg and negative HBsAb, reflex testing for plasma HBV DNA (if positive, reflex HBeAg). If HBeAg is performed and found to be negative, reflex HBeAb
- Hepatitis C virus (HCVAb) serology. Participants who are HCVAb positive will have a HCV RNA test performed

- Obtain urine samples for the following laboratory assessments:
  - Urinalysis
  - Drug and alcohol screening
- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form

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

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

6.3. Subject Enrollment

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

6.4. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. **The Investigator must have confirmed eligibility before proceeding with the Day 1 visit.**

- 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 samples for the following laboratory analyses:
  - 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 participants with total amylase > 1.5 × ULN), and TSH
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula
  - Hematology Profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
  - CD4+ cell count
- Obtain urine samples for the following laboratory assessments:
  - Urinalysis
  - Drug and alcohol screening
- Dispense FDC of B/F/TAF

- Participants should be instructed to take FDC of B/F/TAF without regard to food (except as noted in Table 5-1). The participant should be counseled regarding the importance of adherence and taking their study medication at approximately the same time each day as directed by the Investigator

- Provide a dosing diary to all participants for iPK sample collection

6.5. Treatment Assessments

6.5.1. Maternal treatment assessments (Weeks 4-24 visits, Delivery Visit and Weeks 6 and 12 Post-partum visits)

After completion of the Day 1 Visit, participants will return for Weeks 4, 8, 12, 16, 20 and 24 visits dependent on time of enrollment and when delivery may occur. The day of delivery will be considered as the Delivery Visit for study purposes. After the delivery participants will return for Weeks 6 and 12 post-partum visits.

Study visits are to be completed within ± 2 days of the protocol-specific visit date based on the Day 1 visit until delivery and within ± 2 days based on the date of delivery during the post-partum period of the study.

The following assessments will be completed at all visits unless otherwise specified.

- Review of AEs and changes in concomitant medications

- Complete physical exam:

  — Weeks 4 and 12

  — Weeks 6 and 12 post-partum

- Symptom-driven physical exam: Weeks 8, 16, 20 and 24

- Vital signs (blood pressure, heart rate, respiration rate, and body temperature) including weight

- Obtain blood samples for the following laboratory analyses

  — 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 participants with total amylase > 1.5 × ULN), and TSH (Weeks 12 and 24, and Weeks 6 and 12 post-partum)

  — Estimated glomerular filtration rate according to the Cockcroft-Gault formula (Weeks 12 and 24, and Weeks 6 and 12 post-partum)

- Hematology Profile: complete blood count (CBC) with differential and platelet count (Weeks 12 and 24, and Weeks 6 and 12 post-partum)
- Plasma HIV-1 RNA
- CD4+ cell count: Week 12 post-partum only
- Intensive pharmacokinetic (iPK) evaluations will be completed as noted in Section 6.5.3.
- Plasma storage samples for safety, virology or PK testing (except at Screening, Delivery Visit and 30-Day Follow-up Visit)
- For participants enrolled at sites that can process PBMC samples, a trough PBMC sample will be collected 24 hours following the in-clinic dose administered at the iPK visits.

- Obtain urine samples for the following laboratory assessments:
  - Urinalysis (Weeks 12 and 24, and Weeks 6 and 12 post-partum)
  - Urine pregnancy test (Week 6 and 12 post-partum): positive urine pregnancy tests will be confirmed with a serum test. If the test is positive, the subject will be discontinued
- Document dispensation and accountability of FDC of B/F/TAF

The following assessments will be completed at the Delivery Visit:

- Date of delivery will be collected
- Outcome of the pregnancy will be collected
- Plasma sample for HIV-1 RNA will be obtained
- Additionally Sparse PK samples will be collected per section 6.5.3

6.5.2. Neonatal assessments

Infants will be followed from birth to 4-8 weeks of age if enrolled. The following assessments will be completed at birth and once between 4 to 8 weeks of age unless otherwise specified:

- Complete physical exam
- Adverse Events
- Vital signs (heart rate, respiration rate, and body temperature)
- Apgar scoring: at 5 and 10 minutes after delivery, if recorded

- Anthropometric measures: Head circumference, weight and length
- Blood samples will be collected for PK evaluation as noted in Section 6.5.3.
- HIV-1 RNA and safety assessments (CBC and LFT (ALT, AST, total and direct bilirubin) may be completed using the sparse PK samples collected on the day of birth, if there is sufficient volume. If blood volume is insufficient, results from testing performed per standard of care will be obtained.
- HIV-1 RNA and safety assessments (CBC and LFT (ALT, AST, total and direct bilirubin) may be completed between 4 to 8 weeks of age or results from testing performed per standard of care between 4 to 8 weeks of age will be obtained.
    - If the neonate is HIV-1 positive, additional genotypic assay may be completed if there is sufficient blood volume.

6.5.3. Pharmacokinetic Evaluations

6.5.3.1. Intensive Pharmacokinetic Evaluations

- PK collection during pregnancy:
    - Intensive PK (iPK) visits will be completed after subject has been taking B/F/TAF for at least 3 weeks after Day 1 Visit (i.e after Day 21)
    - For participants who enroll during the second trimester, serial blood samples for iPK evaluation will be collected at or between 20 to 28 weeks of gestation, and during the third trimester, at or between 30 to 38 weeks of gestation.
    - For participants who enroll during the third trimester, serial blood samples for iPK evaluation will be collected at or between 30 to 38 weeks of gestation.
- PK collection post-partum:
    - For all participants, serial blood samples for iPK evaluation will be collected at Weeks 6 and 12 post-partum visits
- Blood samples will be collected at the following time points at each iPK visit:
    - Pre-dose (≤ 5 minutes prior to dosing),
    - 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose
    - A single anytime PK sample will be collected at the ESDD visit, if applicable

- On the days of iPK sampling, study drug will be administered in the morning in the clinic. Following study drug administration participants will fast until after collection of the 2-hour PK sample. Additionally, participants will be restricted from water consumption 1 hour before and 1 hour after study drug administration (except for the 240 mL given with the study drug).

- If a subject is unable to fast for the iPK visit, the visit may proceed, participants should be consistent if they choose to fast or not fast during the iPK visits (i.e. if the subject fasts at the first iPK visit, then they should fast at all other iPK visits).

- Subject dosing diary will be provided to all participants to record the time of study drug administration prior to the iPK visit. Completed dosing diaries will be collected from participants on the day of the iPK Visit. 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.

6.5.3.2. Sparse PK Sample Collection at the Delivery Visit:

- A single maternal blood sample and an umbilical cord blood sample after cord clamping will be collected soon after delivery.

6.5.3.3. Sparse PK Sample Collection for the enrolled neonates:

- Blood samples will be collected at the following time points, if possible: at or between 0 to < 2 hours, 2 to < 3 hours, 3 to 8 hours, 18 to 28 hours, 36 to 72 hours, and 5 to 7 days after birth. These time points may vary based on birth weight, additional instructions will be included in the Pharmacokinetic Sample Collection and Processing Instructions Manual.

6.6. Post-treatment Assessments

6.7. Early Study Drug Discontinuation Assessments

If a subject discontinues their study drug administration prior to the Week 12 post-partum visit, the subject will be asked to return to the clinic within 72 hours of stopping study treatment for the Early Study Drug Discontinuation Visit. The subject will be asked to continue attending the scheduled study visits through the Week 12 post-partum visit. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

At the ESDD Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study treatment, will be repeated until the abnormality is resolved (returns to the baseline value) or is otherwise explained.

The following assessments will be completed at the ESDD Visit.

- Review of AEs and changes in concomitant medications

- Complete physical exam

- Vital signs (blood pressure, heart rate, respiration rate, and body temperature) including weight

- Obtain blood samples for the following laboratory analyses

  — 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 participants with total amylase > 1.5 × ULN), and TSH

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

  — Plasma HIV-1 RNA

  — Pharmacokinetic assessments as noted in Section 6.5.3

- Obtain urine samples for the following laboratory assessments:

  — Urinalysis

  — Urine pregnancy test (if the ESDD visit is after the delivery and if testing is clinically appropriate)

6.7.1. 30-Day Follow-up Visit

Participants who complete the study through their Week 12 post-partum Visit will be required to return to the clinic 30 days after their Week 12 post-partum Visit for a 30-Day Follow-Up Visit.

Participants who prematurely discontinue study treatment and refuse to continue in the study through the Week 12 post-partum Visit will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-up Visit.

Those participants who prematurely discontinue study treatment and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30-Day Follow-up Visit.

For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6-day 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 samples for the following laboratory analyses
  - 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 participants with total amylase > 1.5 × ULN), and TSH
  - Hematology Profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA
- Obtain urine samples for the following laboratory assessments:
  - Urinalysis
  - Urine pregnancy test (positive urine pregnancy tests will be confirmed with a serum test).

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

6.8. Criteria for Discontinuation of Study Treatment

Study medication 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.
- Unacceptable toxicity, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Lack of efficacy

- Subject request to discontinue for any reason
- 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)

6.9. End of Study

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

6.10. Post Study Care

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

6.11. Virologic Failure

Virologic failure is defined as confirmed virologic rebound of HIV-1 RNA ≥ 50 copies/mL at 2 consecutive visits.

6.11.1. Management of Virologic Rebound

Participants who meet the criteria listed below will be considered to have virologic rebound (VR):

- At any post Day 1 visit, a rebound in 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 available plasma samples. If the repeat result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL participants 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 VR) for confirmation of VR.

If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. If resistance to study treatment is detected subject may be discontinued at Investigator's discretion or per local treatment guidelines.

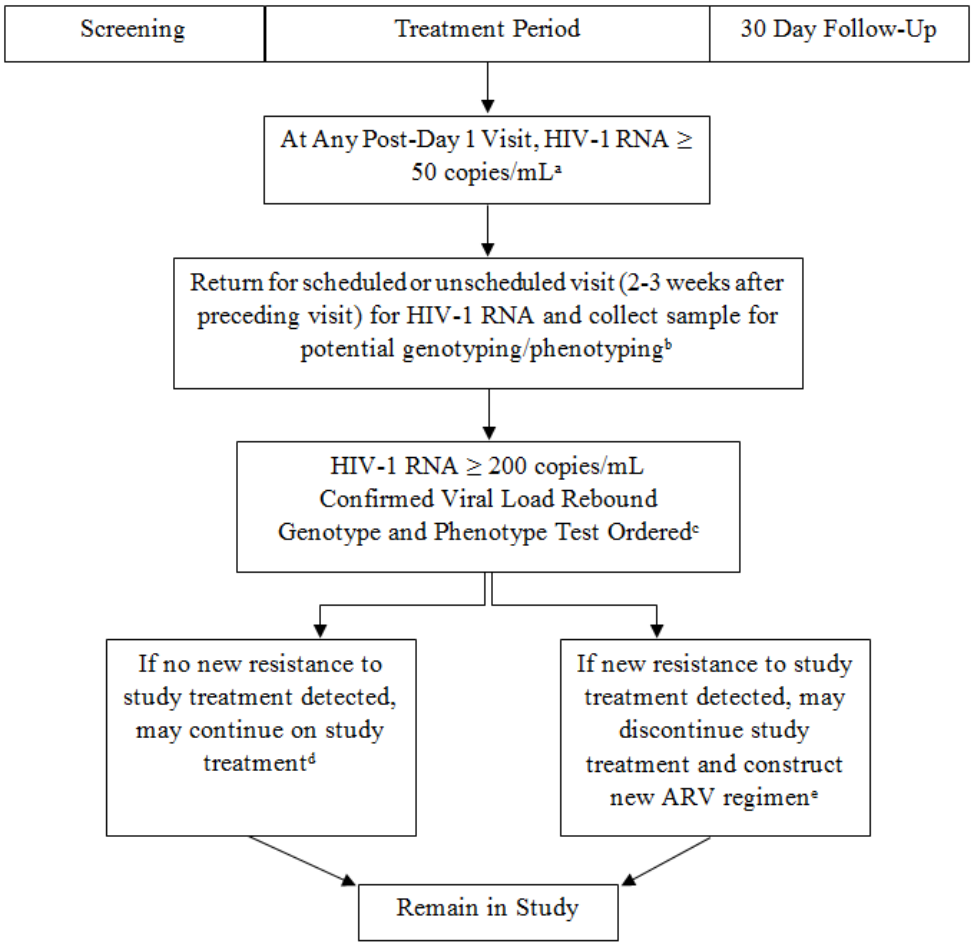
If no resistance to study treatment is detected from the genotype or phenotype, the participant may remain on study treatment and HIV-1 RNA should be analyzed at a new visit (within 2 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and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

6.11.1.1. Participants with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation

Participants with HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation or last visit will be considered virologic failures and will be asked to return for an unscheduled visit within 2 to 3 weeks for a retest.

Participants with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation or last visit will also have resistance testing conducted.

Figure 6-1. Virologic Rebound Schema



a. If the HIV-1 RNA is between 50 and 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on available plasma samples. If the repeat result is < 50 copies/mL, then no further action is required. If the repeat result is ≥ 50 copies/mL then proceed to the scheduled or unscheduled visit 2 – 3 weeks later.
b. If the retest result is < 50 copies/mL, then no further action is required. If the retest result is > 50 copies/mL this is protocol defined confirmed virologic failure and the Medical Monitor should be consulted.
c. If virologic rebound is confirmed and the last HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed. If the genotype and phenotype assay fails, Investigator reviews study treatment continuation/discontinuation options and discuss with the Medical Monitor prior to study treatment discontinuation.
d. If no new resistance to study treatment is detected, HIV-1 RNA will be repeated 2 – 3 weeks later. Investigator reviews study treatment continuation/discontinuation options and discuss with the Medical Monitor prior to study treatment discontinuation. The participant will remain in the study.
e. A new ARV regimen may be configured, at the Investigator's discretion and the participant will remain in the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg. hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is 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.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

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

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

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

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the electronic 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 occur 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 PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- 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 for any reason it is not possible to record and submit the SAE information electronically, i.e. because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper serious adverse event report form and submit by e-mail or fax within 24 hours of the Investigator's knowledge of the event to:

Gilead PVE contact information: Email: PPD
Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax only when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

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

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

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. 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).

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

7.6. Toxicity Management

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

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

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

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

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

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

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

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

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

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

- Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to study drug.

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

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints regardless of an associated AE, outcome of the pregnancy during the study, and pregnancy reports during the post-partum period of the study, an AE in an infant following exposure from breastfeeding, and an occupational exposure with an 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.

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The Investigator should report the outcome of the study related pregnancy to Gilead PVE within 24 hours of awareness of the outcome.

Additionally, the Investigator should report pregnancies that are identified during the post-partum period of the study through 7 days post last study drug dosage to Gilead PVE, using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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 7.1.1 and 7.1.2. 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 any additional pregnancy occurring during the post-partum period while still enrolled in the study. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the post-delivery 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
Fax: PPD

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

7.7.2.2. Reporting Other Special Situations

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

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the steady state PK of BIC and confirm the dose of B/F/TAF 50/200/25 mg FDC in the second and third trimesters of pregnancy

The secondary objectives of this study are:

- To evaluate the steady state PK of FTC and TAF in the second and third trimesters of pregnancy
- To evaluate maintenance of HIV-1 virologic suppression in pregnant women receiving the B/F/TAF FDC during the second and/or third trimesters

The exploratory objectives of this study are as follows:

- To assess frequency of HIV-1 transmission from pregnant women taking B/F/TAF during the second and third trimesters to the neonate
- To evaluate the safety and tolerability of the B/F/TAF FDC in HIV-1 infected virologically suppressed pregnant women during the second and third trimesters through post-partum
- To evaluate the safety of B/F/TAF in neonates with in utero exposure to B/F/TAF
- To explore the PK of TFV-DP in PBMCs in pregnancy following administration of the B/F/TAF FDC
- To explore the elimination of BIC and TAF in neonates from in utero exposure
- To explore placental transfer of BIC and TAF

8.1.2. Primary Endpoint

The primary endpoint is the PK parameter AUC_{tau} of BIC during the second and/or third trimesters through post-partum.

8.1.3. Secondary Endpoint

Secondary endpoints include:

- The PK parameter AUC_{tau} for FTC and TAF, and PK parameters AUC_{last}, C_{max}, C_{tau}, $C_{last,}$, T_{max}, $T_{1/2}$, CL/F, V_z/F and λ_z for BIC, FTC and TAF, as applicable
- The proportion of participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery by missing = excluded approach.

8.1.4. Other Endpoints of Interest

Other endpoints of interest include the PK of PBMC-associated TFV-DP, cord blood to maternal plasma concentration ratio for BIC and TAF, as applicable and BIC and TAF $T_{1/2}$ in infants, where possible. They also include the incidence of AEs and laboratory abnormality in infants.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Enrolled

The All Enrolled analysis set includes all participants who are enrolled into the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Safety Analysis Set

The primary analysis set for safety analyses is defined as safety analysis set, which will include all participants who (1) enroll into the study and (2) have received at least 1 dose of study drug (ie, B/F/TAF). All the data collected up to 30 days after participants permanently discontinue their study drug will be included in the safety summaries, unless specified otherwise.

8.2.1.3. Efficacy

The primary analysis set for efficacy analyses is defined as full analysis set (FAS), which will include all participants who (1) enroll into the study and (2) have received at least 1 dose of study drug (ie, B/F/TAF).

8.2.1.4. Pharmacokinetics

Maternal: The primary analysis set for PK analyses is defined as the PK analysis set, which will include all participants who (1) enroll into the study, (2) have received at least 1 dose of study drug (ie, B/F/TAF), and (3) have at least 1 nonmissing PK concentration data for any analyte of interest reported by the PK lab.

Infant: The PK analysis set for infant will include all infants who (1) enroll into the study, (2) have at least 1 nonmissing PK concentration data for any analyte of interest reported by the PK lab.

8.3. Data Handling Conventions

HIV-1 RNA results of 'No HIV-1 RNA detected' and '< 20 cp/mL HIV-1 RNA Detected' will be imputed as 19 copies/mL for analysis purpose. Logarithm (base 10) transformation will be applied to HIV-1 RNA values for efficacy analysis.

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

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

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

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements 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 summaries will include sex, race, ethnicity, and age.

Baseline data will include a summary of body weight, height, body mass index, eGFR, and HIV-1 infection.

8.5. Efficacy Analysis

The primary efficacy endpoint is the proportion of participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery. It will be analyzed using the missing = excluded approach for imputing missing HIV-1 RNA values: all missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for the percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit.

The 95% CI of the proportion of participants with HIV-1 RNA < 50 copies/mL will be provided using the Clopper-Pearson Exact method.

The efficacy data for infants may be summarized if applicable.

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 dispensed up to the date of last dose of the study drug plus 30 days will be summarized for participants in the safety analysis set. Data for the pretreatment will be included in data listings for all enrolled participants.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug (ie, Gilead dispensed B/F/TAF) will be generated from the study drug administration data. Exposure data will be summarized.

Duration of exposure to study drug will be expressed as the number of weeks between the first and the last dose of B/F/TAF, inclusive, regardless of temporary interruptions in study drug administration.

Dosing information for individual participants will be listed.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event with onset date on or after the study 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 participants) of treatment-emergent adverse events (by SOC, and PT) will be provided. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

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

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

8.6.3. Laboratory Evaluations

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

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

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

Laboratory abnormalities that occur before the first dose of 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. Safety data for infants might be summarized if necessary.

8.7. Pharmacokinetic Analysis

Maternal:

Plasma concentrations of BIC, FTC, and TAF will be summarized by nominal sampling time using descriptive statistics. Pharmacokinetic parameters (AUCtau, Cmax, Ctau, Tmax, and T½, as appropriate) will be listed and summarized for BIC, FTC, and TAF using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, SD, median, Q1, Q3, minimum, and maximum). Plasma concentrations over time will be plotted in semi logarithmic and linear formats as mean ± SD, and median (Q1, Q3).

In addition, an ANOVA using a mixed-effects model with visit as a fixed effect and subject as a random effect will be fitted to the natural logarithmic transformation of PK parameters (AUC_{tau}, C_{max} and $C_{tau,}$ as applicable) for each analyte of interest (ie, BIC, FTC, and TAF). Two-sided 90% CIs will be calculated for the ratios of GLSMs between pregnancy (second and third trimesters) and post-partum (6 and 12 weeks after delivery, respectively).

Table 8-1. Statistical Comparisons for Pharmacokinetic Analyses

Analytes	PK Parameter	Comparison		No Effect Boundary for Lower Bound of 90% CI
		Test	Reference	
BIC	AUC_{tau} C_{max} C_{tau}	Second Trimester	12 Weeks post-partum	> 50%
BIC	AUC_{tau} C_{max} C_{tau}	Third Trimester	12 Weeks post-partum	> 50%
BIC	AUC_{tau} C_{max} C_{tau}	Second Trimester	6 Weeks post-partum	> 50%
BIC	AUC_{tau} C_{max} C_{tau}	Third Trimester	6 Weeks post-partum	> 50%

Infant:

Plasma concentration of BIC will be summarized by nominal sampling time using descriptive statistics. The terminal half-life of BIC will be calculated, where possible, and summarized.

The cord blood to maternal plasma concentrations ratio for BIC and TAF, as applicable, will be calculated, where possible, and summarized.

8.8. Sample Size

With 20 evaluable participants, the study has at least 74% power to show that the lower bound of the 90% CI of the ratio for AUC_{tau} of BIC during pregnancy relative to post-partum is > 50%, assuming a decrease of 40% in AUC_{tau} of BIC during pregnancy relative to post-partum. It was assumed that a standard deviation (SD) of BIC AUC_{tau} is no more than 0.34 on a natural logarithm scale, which is supported by a pooled PK analysis from 4 previous Gilead B/F/TAF Phase 3 studies. With 25% overage, a total sample size of at least 25 participants will be required.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) Good Clinical Practices and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide 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.

9.1.3. 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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study, including the infants who may enroll, 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 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. The consent form will inform participants about pharmacogenomic testing

and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.5. Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) 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 participants screened and for all participants 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's 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.

9.1.6. Study Files and Retention of Records

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

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

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

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

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

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

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

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

9.1.7. 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 9.1.6.

9.1.8. Investigational Medicinal Product Accountability and Return

Where possible, IMP should be destroyed at the site. If the site has an appropriate 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.

If the site does not have an appropriate SOP for drug destruction, used and unused IMP supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

9.1.9. Inspections

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

9.1.10. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

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 participants' interests.

10. REFERENCES

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

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

Colbers AP, Hawkins DA, Gingelmaier A, Kabeya K, Rockstroh JK, Wyen C, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. AIDS 2013;27 (5):739-48.

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

Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014;5:65.

Gilbert EM, Darin KM, Scarsi KK, McLaughlin MM. Antiretroviral Pharmacokinetics in Pregnant Women. Pharmacotherapy 2015;35 (9):838-55.

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

Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, et al. Effects of Pregnancy on CYP3A and P-glycoprotein Activities as Measured by Disposition of Midazolam and Digoxin: A University of Washington Specialized Center of Research Study. Clin Pharmacol Ther 2008;84 (2):248-53.

Isoherranen N, Thummel KE. Drug Metabolism and Transport During Pregnancy: How Does Drug Disposition Change during Pregnancy and What Are the Mechanisms that Cause Such Changes? Drug Metab Dispos 2013;41 (2):256-62.

Jeong S, Nguyen PD, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. Antimicrob Agents Chemother 2009;53 (2):541-51.

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

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

Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clin Pharmacokinet 1997;33 (5).

Lutz J, Shao Y, Ling J, Custodio J, Martin H, Quirk E, et al. Bictegravir/Emtricitabine/Tenofovir Alafenamide Phase 3 Exposure-Response Analysis of Safety and Efficacy in the Treatment of HIV Infection [Poster 6]. 19th International Workshop on Clinical Pharmacology of Antiviral Therapy, May 22–24; 2018 May 22–24; Baltimore, Maryland.

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

Mulligan N, Best BM, Wang J, Capparelli EV, Stek A, Barr E, et al. Dolutegravir Pharmacokinetics in Pregnant and Postpartum Women Living with HIV. AIDS 2018;32 (6):729-37.

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

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

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Last Updated: 7 December. 2018.

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.

Stek A, Best B, Luo W, Capparelli E, Burchett S, Hu C, et al. Effect of pregnancy on emtricitabine pharmacokinetics. HIV Med 2012;13 (4):226-35.

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

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

Watts D, Stek A, Best B, Wang J, Capparelli E, Cressey T, et al. Raltegravir Pharmacokinetics during Pregnancy [Author Manuscript]. J Acquir Immune Defic Syndr. 2014;67 (4):375-81.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1b, Open-label study to Evaluate the PK, Safety and Efficacy of B/F/TAF in HIV-1 infected, Virologically Suppressed, Pregnant Women in their Second and Third Trimesters

GS-US-380-5310 Original, 02 April 2019

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

PPD

PPD

PPD

Signature

03 April 2019

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Maternal and Neonatal Study Procedures Tables

Maternal Study Procedures Table

Study Procedure	Screening	Day 1	Visits before the delivery		Delivery Visit[j]	Post-partum Visit		30-Day Follow-up Visit	ESDD
			Week 4	Weeks 8, 12, 16, 20 & 24 (dependent on time of enrollment)[a]		Week 6	Week 12		
Written Informed Consent	X								
Medical History	X								
Complete Physical Examination[b]	X	X	X	X[b]		X	X		X
ECG	X								
Symptom-directed Physical Examination[c]				X[c]				X	
Vital Signs (including weight)	X	X	X	X		X	X	X	X
Height	X								
Laboratory Assessments[d]	X	X		X[d]		X	X	X	X
Maternal alfa-fetoprotein level	X								
Urine Pregnancy Test[e]						X	X	X	X
eGFR[f]	X	X		X[e]		X	X		
HIV-1 RNA	X	X	X	X	X	X	X	X	X

Study Procedure	Screening	Day 1	Visits before the delivery		Delivery Visit[j]	Post-partum Visit		30-Day Follow-up Visit	ESDD
			Week 4	Weeks 8, 12, 16, 20 & 24 (dependent on time of enrollment)[a]		Week 6	Week 12		
Whole Blood Sample for HIV-1 Genotyping[g]	X								
CD4+ cell count	X	X					X		
HBV and HCV Testing	X								
Ultrasound[h]	X								
Intensive PK Sample Collection[i, j]			X	X		X	X		
Sparse PK Sample Collection[k]					X				
Plasma Storage Sample		X	X	X		X	X		X
PBMC Sample Collection[l]			X	X		X	X		
Drug and Alcohol Screening	X	X							
Adverse Event and Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Date of Delivery					X				
Pregnancy outcome					X				
B/F/TAF Dispensation		X	X	X	X	X			
B/F/TAF Accountability			X	X		X	X		X

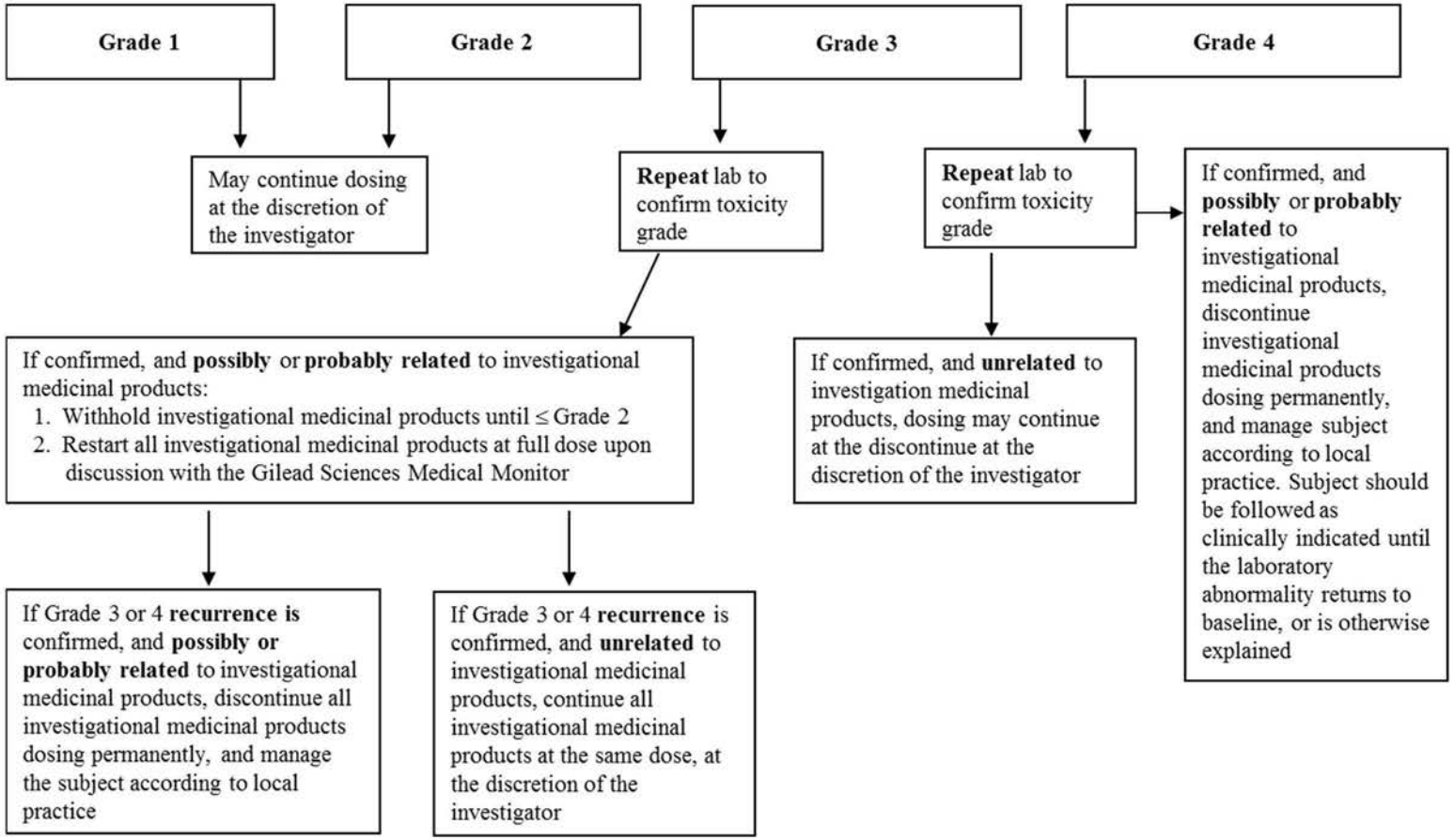
a. After completion of the Week 4 visit, participants will be required to come back for a study visit every 4 weeks (Weeks 8, 12, 16, 20, 24 dependent on time of enrollment and time of delivery). Study visits may be completed within ± 2 days of protocol-specified visit date.
b. A complete physical examination will be completed at Day 1, Week 4, Week 12 and Weeks 6 and 12 post-partum visits, and at the ESDD visit.
c. A symptom directed physical examination will be completed at Weeks 8, 16, 20 and 24 visits and at the 30-Day Follow-up Visit.
d. Clinical laboratory assessments include hematology, chemistry and urinalysis which will be completed at Screening, Day 1, Weeks 12 and 24, Weeks 6 and 12 post-partum visits, 30-Day Follow-up Visit and ESDD Visit.
e. Urine pregnancy testing will be completed at the ESDD if it is clinical appropriate and the subject is in the post-partum phase of the study.
f. eGFR will be calculated at Screening, Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits.
g. Sample may be collected at Screening OR Day 1.
h. Ultrasound should be completed prior to the Day 1 visit. An ultrasound completed prior to the screening visit is acceptable.
i. Before delivery, Intensive PK sample collection will be completed after subject administers B/F/TAF for at-least 3 weeks. For participants enrolled during the second trimester, iPK sample collection will be completed at or between 20 to 28 weeks of gestation and at or between 30 to 38 weeks of gestation. For participants enrolled during the third trimester, iPK sample collection will be completed at or between 30 to 38 weeks of gestation.
j. After delivery, iPK sample collection will be completed at Week 6 and Week 12 post-partum visits.
k. A single maternal blood sample and an umbilical cord sample after cord clamping will be collected at the time of delivery (Delivery Visit).
l. For participants enrolled at sites that can process PBMC samples, a trough PBMC sample will be collected 24 hours following the in-clinic dose administered at the iPK visits.
m. The day of delivery will be considered as the Delivery Visit for study purposes.

Neonatal Study Procedures Table

Study Procedure	Delivery Visit	4-8 Weeks of age
Complete Physical Examination	X	X
Vital signs	X	X
Apgar score[n]	X	
Anthropometric measures[o]	X	X
HIV-1 RNA and Safety Assessments[p]	X	X
Sparse PK Sample Collection[q]	X	

n. Apgar score will be collected if it is recorded at the time of birth per standard of care
o. Head circumference, weight and length at birth and 4-8 weeks of age will be collected
p. HIV-1 RNA and safety assessments which includes CBC, LFTs (ALT, AST, total and direct bilirubin) may be completed using the sparse PK samples collected on the day of birth, if there is sufficient volume. If blood volume is insufficient, results from testing performed per standard of care will be obtained. HIV-1 RNA and safety assessments will also be completed at 4-8 weeks of age if possible or results from testing performed per standard of care will be obtained.
q. Sparse PK blood samples will be collected at the following time points, if possible: at or between 0 to < 2 hours, 2 to < 3 hours, 3 to 8 hours, 18 to 28 hours, 36 to 72 hours, and 5 to 7 days after birth. These time points may vary based on birth weight, additional instructions will be included in the Pharmacokinetic Sample Collection and Processing Instructions Manual.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL51681 < 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male participants >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 5. 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

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

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

1) Definitions

a. Definition of Childbearing Potential

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

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

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

2) Post-partum Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of B/F/TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of B/F/TAF have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are currently no other clinical studies of B/F/TAF in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

b. Post-partum Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female Participants of childbearing potential requires using at least an acceptable effective contraceptive measure during the postpartum period until the end of study. The appropriate contraceptive measure and timing of initiation for women who are postpartum should be discussed with the healthcare provider managing the patient in the postpartum period. In the event of a delayed menstrual period after the resumption of menses in the postpartum period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from postpartum until 7 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 3 months after procedure)
- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
- Barrier methods (one female barrier and one male barrier must be used in combination)
  - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Male barriers: Male condom (with or without spermicide)
- Hormonal methods
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Participants must also refrain from egg donation and in vitro fertilization during treatment and until at least 7 days after the last dose of study drug.

3) Unacceptable Birth Control Methods During the Post-partum Period

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

4) Procedures to be Followed in the Event of Pregnancy During the Post-partum Period

Participants will be instructed to notify the investigator if they become pregnant during the post-partum period of the study, or if they become pregnant within 7 days of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the post-partum period must report the information to the investigator and discontinue study drug immediately. Instructions for reporting pregnancy and pregnancy outcomes that occur during the post-partum period of the study are outlined in Section 7.7.2.1.