CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Randomized, Double-Blinded, Placebo Controlled, Multi-Cohort Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-6207 administered subcutaneously in HIV-1 Infected Subjects	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	136260	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT03739866	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-200-4072	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
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Gilead Clinical Study Director:	Name: Telephone: Fax: Cell:	PPD PPD PPD PPD
Protocol Version/Date:	Original : Amendment 1: Amendment 2: Amendment 3: Amendment 4:	14 September 2018 20 December 2018 13 March 2019 21 May 2019 13 June 2019

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1b Randomized, Double-Blinded, Placebo Controlled, Multi-Cohort Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-6207 administered subcutaneously in HIV-1 Infected Subjects
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	136260 Not Applicable NCT03739866
Study Centers Planned:	Approximately 15 centers in United States.
Objectives:	**Part A (Cohorts 1 – 5)** The primary objective of this study is as follows: • To evaluate the short-term antiviral activity of GS-6207 compared to placebo GS-6207, with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but capsid inhibitor (CAI) naïve. The secondary objectives of this study are as follows: • To investigate the safety and tolerability of GS-6207 as compared to placebo GS-6207 in HIV-1 infected subjects. • To characterize the plasma pharmacokinetics (PK) of GS-6207 in HIV-1 infected subjects. • To characterize the PK/pharmacodynamics relationship between GS-6207 concentration and the viral dynamics of HIV-1. • To determine the number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 at each dose level. • To examine any emergence of capsid inhibitor (CAI) resistance.

Part B (Cohorts 6 – 8)

The primary objective of this study is as follows:

- To evaluate the short-term antiviral activity of TAF with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but without resistance to TAF.

The secondary objectives of this study are as follows:

- To investigate the safety and tolerability of TAF in HIV-1 infected subjects.
- To characterize the pharmacokinetics (PK) of TAF and its metabolites in HIV-1 infected subjects.
- To examine any emergence of TAF resistance.

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Study Design:	Randomized, double-blinded, placebo-controlled, multi-cohort study of GS-6207 (Part A) and single arm study of TAF (Part B) monotherapy in subjects with HIV-1 infection.
Number of Participants Planned:	Approximately 64
Target Population:	HIV-1 infected subjects who are antiretroviral treatment naïve or experienced but integrase strand transfer inhibitor (INSTI) naïve and CAI naïve (Part A only), have not received any antiretroviral therapy (ART) within 12 weeks of screening, and have genotypic sensitivity to B/F/TAF (single tablet regimen of bictegravir/emtricitabine/tenofovir alafenamide)
Duration of Treatment:	Single dose (Day 1)
Diagnosis and Main Eligibility Criteria:	Subjects with chronic HIV-1 infection and meet the following criteria: • Plasma HIV-1 RNA ≥ 5,000 copies/mL but ≤ 400,000 copies/mL and CD4+ cell count > 200 cells/mm^3 • Treatment naïve or experienced but integrase strand transfer inhibitor (INSTI) naïve and CAI naive (Part A only), and have not received any ART within 12 weeks of screening

- Screening genotype report must show sensitivity to B/F/TAF to allow TAF monotherapy (Part B) and initiation of B/F/TAF on Day 10 (Part A and Part B)
- Screening genotype report must show sensitivity to at least one agent in either non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) class to allow its use as part of standard of care oral antiretroviral treatment in the future
- Have adequate renal function (estimated GFR ≥ 70 mL/min)
- No clinically significant abnormalities in ECG at Screening
- Not pregnant or lactating
- Willing to initiate B/F/TAF on Day 10 after completion of all assessments

Study Procedures/ Frequency:

This study may enroll up to 5 cohorts in Part A and up to 3 cohorts in Part B, of approximately 8 unique subjects per cohort. All subjects will be enrolled after the completion of screening procedures and following confirmation of study eligibility. Within each Cohort (n=8) in Part A, subjects will be randomized in a 3:1 ratio to receive active GS-6207 (n=6) or placebo (n=2). Within each Cohort (n=8) in Part B, subjects will be enrolled to receive active oral TAF.

Part A: A single dose of GS-6207 or placebo will be administered subcutaneously (SC) in the abdomen on Day 1. GS-6207 doses may be administered as multiple SC injections at different abdominal sites, as appropriate. In the case where multiple injections are administered for a given dose, the first and last injections should be no more than 30 minutes apart. If necessary for practical reasons, the period may be extended up to 45 minutes.

Cohort	*Treatment*
1	*150 mg GS-6207 or placebo*
2	*50 mg GS-6207 or placebo*
3	*450 mg GS-6207 or placebo*
4	*20 mg GS-6207 or placebo*
5	*750 mg GS-6207 or placebo*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety and PK data.

The doses to be evaluated in Cohorts 2 through 5 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts as well as available safety (through at least Day 14) and pharmacokinetic data from Study GS-US-200-4070 (Phase 1, first-in-human, single ascending dose study of GS-6207 SC suspension formulation, in which GS-6207 30 to 450 mg was administered subcutaneously). As such, Cohorts 2-5 may be initiated in parallel. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses either in this study or in Study GS-US-200-4070; the same SC suspension formulation is being administered in both studies. The highest proposed dose in this study, GS-6207 900 mg, represents a 2-fold dose escalation over GS-6207 450 mg, which has been shown to be safe and well tolerated in Study GS-US-200-4070, based on a blinded review of safety data.

Observed GS-6207 or placebo (study drug) dosing is required at Day 1.

Part B: A single dose of TAF will be administered orally on Day 1.

Cohort	***Treatment***
6	*200 mg TAF*
7	*Up to 600 mg TAF*
8	*Up to 600 mg TAF*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety and PK data.

The doses to be evaluated in Cohorts 7-8 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses in this study. Cohorts 7 and 8 may be run in parallel.

Observed TAF dosing is required at Day 1.

In Part A, following screening and Day 1 visits, subjects will be required to visit the clinic on Days 2, 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225.

In Part B, following screening and Day 1 visits, subjects will be required to visit the clinic on Days 2, 3, 4, 5 (if possible), 6 (if possible), 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225.

Adverse events, concomitant medications, complete or symptom-directed physical examinations, and HIV-1 RNA will be performed at Screening, Day 1, and all subsequent study visits. CD4+ cell count will be performed at Screening, Day 1, Day 10, and all subsequent study visits. Other laboratory analyses (hematology, chemistry, and urine chemistry) will be performed at Screening, Days 1, 3, 7, 10, 14, and all subsequent study visits. Fasting is required for laboratory analyses at Days 1, 3, 7, 10, 85, 169 and 225.

ECGs will be performed at Screening, Days 1 (pre-dose), 2, 10, 29, 57, 85, 169, and 225.

A plasma sample for genotypic and phenotypic testing of HIV-1 capsid (Part A) or HIV-1 RT (Part B) will be collected at Screening and Day 10 for all subjects to determine eligibility and to evaluate the potential emergence of resistance against GS-6207 (Part A) or TAF (Part B). The screening plasma sample will also be used for genotypic testing of HIV-1 PR, RT, and IN to determine eligibility.

A whole blood sample for potential HIV DNA genotyping will be collected at Days 85, 169 and 225.

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Subjects who meet the criteria for virologic failure after Day 10 will be tested for the potential development of resistance against all components of the treatment regimen, including GS-6207.

GS-6207 PK sampling (Part A, Cohorts 1 –5):

Blood samples will be collected to determine GS-6207 PK (and metabolites, if applicable) in plasma at the following time points relative to study drug dosing:

- Day 1: 0 (pre-dose), 1, 2, 4, 8, 12, and 24 hours post dose.
- Days 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225: a single anytime PK sample will be collected.

TAF PK sampling (Part B, Cohorts 6 - 8):

Plasma PK samples will be collected to determine PK of TAF and its metabolite, TFV, at the following time points relative to study drug dosing:

- Day 1: 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours post dose.
- Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10 at approximately the same time in the morning as pre-dose on Day 1.

	PBMC PK samples will be collected to determine PK of TFV-DP at the following time points relative to study drug dosing: • Day 1: 0 (pre-dose), 1, 2, 4, 6, 8, 12, 24 and 48 hours post dose. • Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10 at approximately the same time in the morning as pre-dose on Day 1. All subjects will initiate B/F/TAF on Day 10 after completion of all assessments.
Test Product, Dose, and Mode of Administration:	**Part A:** Study drug will be administered SC in the morning without regard to food. Observed study drug dosing is required. Cohort 1: GS-6207 150 mg Cohort 2: GS-6207 50 mg Cohort 3: GS-6207 450 mg Cohort 4: GS-6207 20 mg Cohort 5: GS-6207 750 mg **Part B:** Study drug will be administered orally in the morning under fasted conditions. Observed study drug dosing is required. Cohort 6: TAF 200 mg Cohort 7: TAF up to 600 mg Cohort 8: TAF up to 600 mg
Reference Therapy, Dose, and Mode of Administration:	**Part A:** Study drug will be administered SC in the morning without regard to food. Observed study drug dosing is required. Cohort 1: Placebo GS-6207 150 mg Cohort 2: Placebo GS-6207 50 mg Cohort 3: Placebo GS-6207 450 mg Cohort 4: Placebo GS-6207 20 mg Cohort 5: Placebo GS-6207 750 mg **Part B:** None
Criteria for Evaluation:	
Safety:	Adverse events, vital signs, clinical laboratory tests, ECG

Efficacy:	Maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10
Pharmacokinetics:	**Part A:** The following GS-6207 PK parameters in plasma will be calculated: AUC_{0-t}, AUC_{inf}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, C_{D10}, T_{last} **Part B:** The following PK parameters will be calculated for TAF and TFV in plasma, or TFV-DP in PBMCs, as appropriate: AUC_{0-t}, AUC_{inf}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, C_{D10}, T_{last}
Statistical Methods:	Data from the placebo recipients in all Cohorts will be combined to form one placebo group for analysis purposes. Each GS-6207 (Part A) and TAF (Part B) dose group will be compared to the placebo group in Part A with respect to the efficacy endpoints. Incidence of treatment emergent AEs and graded laboratory toxicities will be summarized by treatment group. GS-6207 and TAF (and metabolites, as applicable) PK parameters will be summarized by treatment group using descriptive statistics. **Part A:** A sample size of 6 subjects in each GS-6207 dose group and a total of 10 subjects in the placebo group will provide 99% power to detect a treatment difference of 2.79 log_{10} copies/mL in maximum reduction of HIV-1 RNA between at least one of the GS6207 dose groups and the placebo group. In this power analysis, it is assumed that a common standard deviation for maximum reduction in HIV-1 RNA is 0.526 log_{10} copies/mL (based on Study GS-US-141-1219) and a 2-sided t-test is conducted at an alpha level of 0.05. **Part B:** A sample size of 8 subjects in each TAF dose group and a total of 10 subjects in the placebo group will provide 99% power to detect a treatment difference of 1.43 log_{10} copies/mL in maximum reduction of HIV-1 RNA between at least one of the TAF dose groups and the placebo group from Part A. In this power analysis, it is assumed that a common standard deviation for maximum reduction in HIV-1 RNA is 0.52 log_{10} copies/mL (based on Studies GS-US-120-0104 and GS-US-120-1101) and a 2-sided t-test is conducted at an alpha level of 0.05.

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
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
B	bictegravir
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BUN	blood urea nitrogen
CAI	capsid inhibitor
CBC	complete blood count
CFR	FDA code of federal regulations
CI	confidence interval
CK	creatine kinase
C_{last}	last measurable plasma concentration
C_{D10}	concentration at Day 10
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRO	contract (or clinical) research organization
CSR	clinical study report
CYP	cytochrome P450
DHHS	Department of Health and Human Services
DLT	Dose-limiting toxicity
DNA	deoxyribonucleic acid
DP	diphosphate
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone

FTC	emtricitabine
GCP	Good Clinical Practice (Guidelines)
GSI, Gilead	Gilead Sciences, Inc.
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBeAB	hepatitis B virus e-antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP, study drug	investigational medicinal products
INSTI	integrase strand-transfer inhibitor
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
KS	Kaposi's sarcoma
LDL	low density lipoprotein
LLT	lower level term
LSM	least-squares mean
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
mtDNA	mitochondrial DNA
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PK	pharmacokinetic
PVE	Phamacovigilance and Epidemiology
PXR	pregnane X receptor
QD	once daily
RNA	ribonucleic acid

RT	reverse transcriptase
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	subcutaneously
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	suboptimal virologic rebound
T_{max}	the maximum time that a drug is present at the maximum concentration in serum
TAF	tenofovir alafenamide
TAM	thymidine analogue mutations
TDF	tenofovir disoproxil fumarate, Viread®
TE	treatment experienced
TFV	tenofovir
T_{last}	time (observed time point) of C_{last}
ULN	upper limit of the normal range
US	United States
USPI	United States prescribing information
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Human Immunodeficiency Virus (HIV)-1 infection is a life-threatening and serious disease of major public health significance, with approximately 37 million people infected worldwide, and approximately 15.8 million on antiretroviral (ARV) treatment {Centers for Disease Control (CDC) 2017, UNAIDS 2016}. Advances in combination antiretroviral therapy (ART) for HIV have led to significant improvements in morbidity and mortality by suppressing viral replication, preserving immunologic function, and averting disease progression to acquired immunodeficiency syndrome (AIDS). Standard-of-care for the treatment of HIV-1 infection involves the use of a combination of oral ARV drugs (ie, 2 NRTIs plus a third agent) to suppress viral replication to below detectable limits, increase CD4 cell counts, and delay disease progression.

While combination ARV therapy for the treatment of HIV-1 infection is efficacious and well tolerated, these agents need to be taken every day and require near perfect adherence to minimize the emergence of drug resistant variants. In addition, "treatment fatigue" can occur, defined as "decreased desire and motivation to maintain vigilance in adhering to a treatment regimen" among patients prescribed chronic or life-long treatment {Claborn 2015}, which can lead to nonadherence and treatment failure. As such, there remains a significant medical need for ARVs that can be administered less frequently (ie, long acting drug products), thereby providing an alternative treatment option for HIV-1 infected individuals.

The viral capsid (CA) protein plays multiple essential roles in the HIV-1 replication cycle, including the assembly and maturation of new virions, the encapsidation of the viral RNA genome and replicative enzymes into a protective conical capsid shell, the controlled disassembly of the capsid shell following viral entry to help coordinate reverse transcription of the viral genome, and the active trafficking of viral DNA to the nucleus via a nuclear pore to enable formation of an integrated provirus.

1.2. GS-6207

GS-6207 is a novel, first-in-class, selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

1.2.1. General Information

For further information on GS-6207, please refer to the investigator's brochure (IB). Information in the IB includes:

- Nonclinical pharmacology and toxicology
- Nonclinical pharmacokinetics (PK) and in vitro metabolism
- Preclinical pharmacology, pharmacokinetics, and toxicology
- Clinical experience

1.2.2. Additional Clinical Studies

As of January 10, 2019, 3 Phase 1 clinical studies in healthy volunteers and 1 study in subjects with HIV infection were ongoing:

GS-US-200-4070, a Phase 1 Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneous GS-6207 (Aqueous Suspension) in Healthy Subjects

GS-US-200-4071, a Phase 1 Study in Healthy Volunteers to Evaluate the Safety, Tolerability and Pharmacokinetics of Oral GS-6207, and the Effect of Food on GS-6207 Pharmacokinetics

GS-US-200-4538, a Phase 1 Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneous GS-6207 (Solution Formulations) in Healthy Subjects

GS-US-200-4072, a Phase 1b randomized, double-blinded, placebo-controlled, multi-cohort study of the safety, pharmacokinetics, and antiviral activity of GS-6207 administered as a subcutaneous injectable suspension in HIV-1 infected subjects.

A brief summary of the available data from these studies is presented.

1.2.2.1. GS-US-200-4070 Summary

Study GS-US-200-4070 is an ongoing, Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single ascending doses of a GS-6207 subcutaneous suspension. 40 unique subjects across 4 dosing cohorts have received either SC GS-6207 or placebo (4:1 ratio). Administration of single SC doses of GS-6207 30 mg (Cohort 1), 100 mg (Cohort 2), 300 mg. (Cohort 3) and 450 mg (Cohort 4) is complete. PK sampling for Cohorts 1 and 2 (through Day 169 [24 weeks] post dose) is complete and ongoing for Cohorts 3 and 4 (through Day 225 [32 weeks] post dose). Preliminary PK profiles and PK parameters of subcutaneous GS-6207 administered as single doses of 30 mg, 100 mg, 300 mg and 450 mg are presented in Figure 1-1 and Table 1-1 below. Preliminary PK data are available for 168 days post dose for Cohorts 1, 2 and 4, and through 196 days post-dose for Cohort 3.

GS-6207 PK profiles (Table 1-1) are consistent with sustained delivery. The PK is characterized by prolonged exposure, with measureable concentrations for up to 196 days [28 weeks], to date. The median apparent terminal $t_{1/2}$ is 30-43 days. Increases in GS-6207 mean C_{max} and AUC_{inf} are approximately dose proportional over the dose range of 30-450 mg.

In a preliminary blinded review of the available safety data through February 1, 2019 (n=40), no deaths, serious adverse events (SAEs), or Grade 3-4 adverse events (AEs) have been reported. Injection site reactions occurred in 21 of 40 subjects (53%) these included injection site erythema (15 subjects, 38%), injection site pain (14 subjects, 35%), injection site nodules (9 subjects, 23%), injection site induration (8 subjects, 20%), and injection site swelling (7 subjects, 18%). The only other AE that was reported by more than 10% of subjects was headache (5/40, 13%).

Figure 1-1. **Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Subcutaneous Suspension of GS-6207 30 mg, 100 mg, 300 mg and 450mg (N=8 per cohort)**

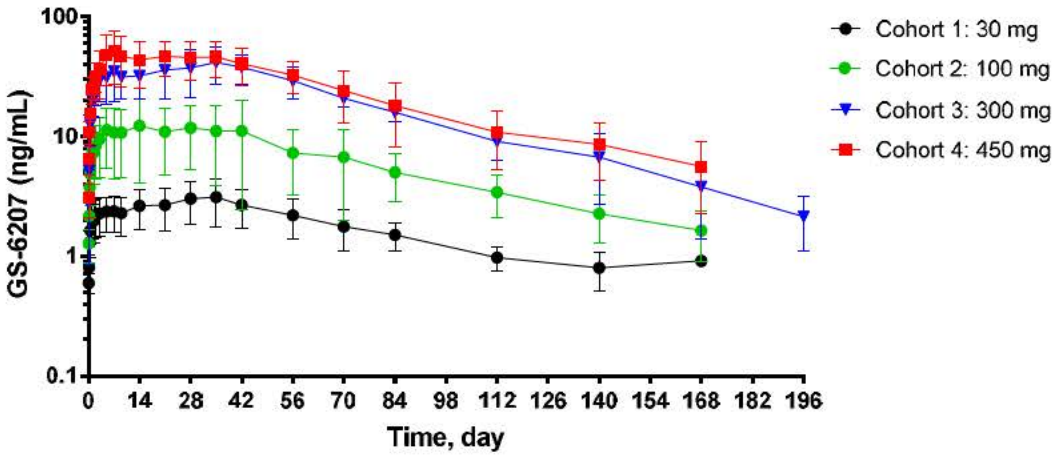


Table 1-1. **Study GS-US-200-4070 Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Single Dose Administration of Subcutaneous Suspension of GS-6207, 30-450 mg**

	Cohort 1 N=8	Cohort 2 N=8	Cohort 3 N=8	Cohort 4 N=8
Dose (Injection Volume)	30 mg (1 x 0.3 mL)	100 mg (1 x 1 mL)	300 mg (3 x 1 mL)	450 mg (3 x 1.5 mL)
PK Parameter Mean (%CV)				
AUC_{inf} (hr*ng/mL)	7740 (8.75)[a]	27600 (40.4)[b]	86300 (18.5)[c]	111000 (25.7)[c]
AUC_{last} (hr*ng/mL)	6800 (13.1)	25900 (44.6)	81300 (18.0)	102000 (21.0)
AUC %Extrapolated (%)	12.3 (36.3)	6.92 (70.5)	5.45 (113)	6.79 (68.4)
C_{max} (ng/mL)	3.24 (39.8)	14.7 (58.4)	47.9 (27.7)	58.4 (22.9)
C_{D10} (ng/mL)	2.28 (36.7)	10.7 (57.7)	31.4 (35.2)	47.1 (44.7)
t_{max} (day)†	35.0 (22.3, 36.8)	21.0 (11.8, 36.8)	31.5 (17.5, 35.0)	14.0 (6.50, 29.8)
$t_{1/2}$ (day)†	35.5 (31.5, 40.2)[a]	30.3 (23.6, 48.2)[b]	43.1 (26.5, 46.5)[c]	39.9 (32.8, 48.8)[c]

Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits
†Median (Q1,Q3); [a] n=4; [b] n=6; [c] n=7; ND= Not yet determined

1.2.2.2. GS-US-200-4071 Summary

Study GS-US-200-4071 is an ongoing, Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single and multiple ascending doses of a GS-6207 oral capsule. As of January 10, 2019, a total of 40 unique subjects have received GS-6207 in Cohorts 1-4.

In Cohorts 1 and 2, each subject was randomized to receive either GS-6207 (N=8; 50 mg/mL) or matching placebo (N=2); a single dose was administered under fasted conditions on Day 1 followed by a 10-day washout period, then 10 days of once-daily doses on Days 11-20.

Preliminary single dose PK profiles from Cohorts 1 and 2 (Figure 1-2) suggested that the 10 day washout period was not sufficient to allow for characterization of the elimination phase following a single oral dose of GS-6207. As a result, the protocol was amended to limit evaluation of GS-6207 PK to single ascending doses with extended PK sampling to allow for characterization of the single dose oral PK prior to any further multiple dosing.

A summary of the preliminary PK parameters of oral GS-6207 after administration of single and multiple doses of 30 mg (50 mg/mL; Cohort 1) and 100 mg (50 mg/mL; Cohort 2) are presented in Table 1-2 below. Maximum plasma concentrations of GS-6207 (C_{max}) occurred between 3.5 and 29 hours (median T_{max}). Following multiple dosing, the mean C_{max} and AUC_{0-24} were at least 10-fold higher than those after a single dose.

Table 1-2. Study GS-US-200-4071 Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Single and Multiple Dose Oral Administration of 30 mg (50 mg/mL) and 100 mg (50 mg/mL)

	Cohort 1 (N=8)		Cohort 2 (N=8)	
	30 mg SD	30 mg MD	100 mg SD	100 mg MD
C_{max} (ng/mL)	1.16 (23.9)	12.2 (17.1)	2.70 (55.4)	41.3 (53.8)
t_{max} (hr)†	29.0 (4.00, 90.0)	3.50 (1.89, 10.0)	26.0 (4.00, 96.0)	4.00 (4.00, 10.5)
AUC_{0-24hr} (hr*ng/mL)	17.6 (19.7)	232 (17.9)	34.8 (47.3)	843 (56.5)
AUC_{last} (hr*ng/mL)	147 (29.0)	-	319 (46.0)	-

Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits
AUC_{0-24hr}= AUC from time zero through 24 hours post dose; AUC_{last} = AUC from time zero to Day 7 post dose for single dose
†Median (Q1,Q3)

In Cohorts 3 and 4, each subject was randomized to receive a single dose of either GS-6207 (N=8; 100 mg/mL) or matching placebo (N=2).

PK profiles and preliminary PK parameters of GS-6207 after administration of single oral doses of 300 mg (100 mg/mL; Cohort 3) and 75 mg (100 mg/mL; Cohort 4) are presented in Figure 1-2 and Table 1-3 below. Maximum plasma concentrations of GS-6207 (C_{max}) occurred between 6.00 and 38 hours (median T_{max}). The increase in C_{max} was less than dose proportional between 75 and 300 mg. Based on the available PK from Cohort 3, the estimated terminal $t_{1/2}$ of GS-6207 is approximately 16 days.

Figure 1-2. **Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-6207 at 30, 100, 300 and 75 mg (N=8/cohort)**

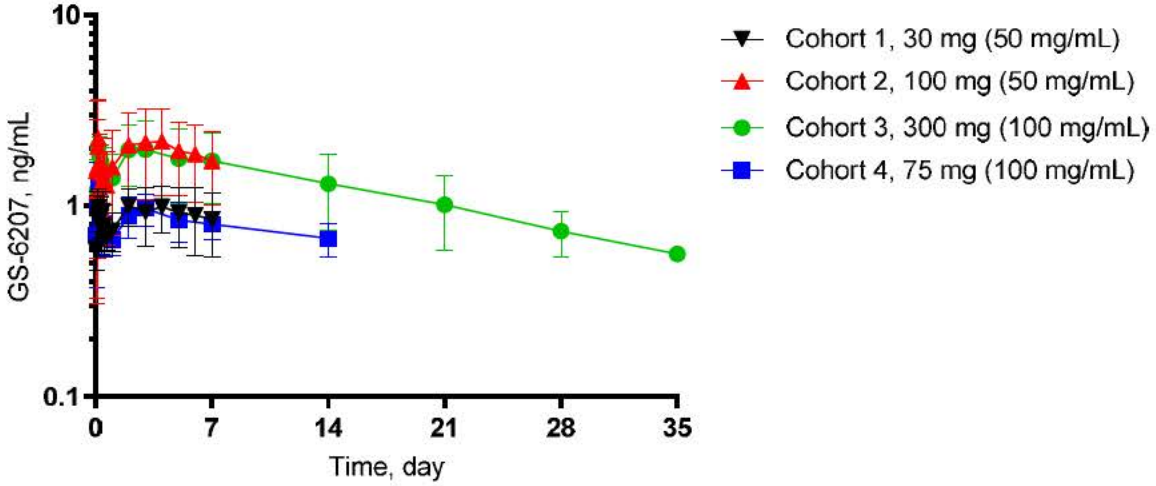


Table 1-3. **Study GS-US-200-4071 Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Single Dose Oral Administration in Cohorts 3 (300 mg, 10 mg/mL) and 4 (7 mg, 100 mg/mL)**

	Cohort 3 (N=8) 300 mg SD	**Cohort 4 (N=8) 75 mg SD**
Parameter		
C_{max} (ng/mL)	2.33 (31.9)	1.33 (41.7)
t_{max} (hr)†	6.00 (4.00, 16.5)	38.0 (4.00-72.0)
AUC_{last} (hr*ng/mL)	877 (46.4)	217 (56.3)
AUC_{inf} (hr*ng/mL)	1200 (29.1)	TBD[a]
AUC %Extrapolated (%)	29.3 (39.9)	52.9 (20.7)
$t_{1/2}$†(days)	15.7 (11.1, 17.5)	TBD[a]

Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits; TBD = to be determined, †Median (Q1,Q3); [a] AUC % extrapolated is currently too large to provide estimates of AUC_{inf} and $t_{1/2}$, parameters will be calculated upon availability of data

In a preliminary blinded review of safety data to date as of January 10, 2019 of Cohorts 1-4, no deaths, serious adverse events (SAEs), or Grade 2-4 adverse events (AEs) have been reported; no AE has been reported in more than 1 subject.

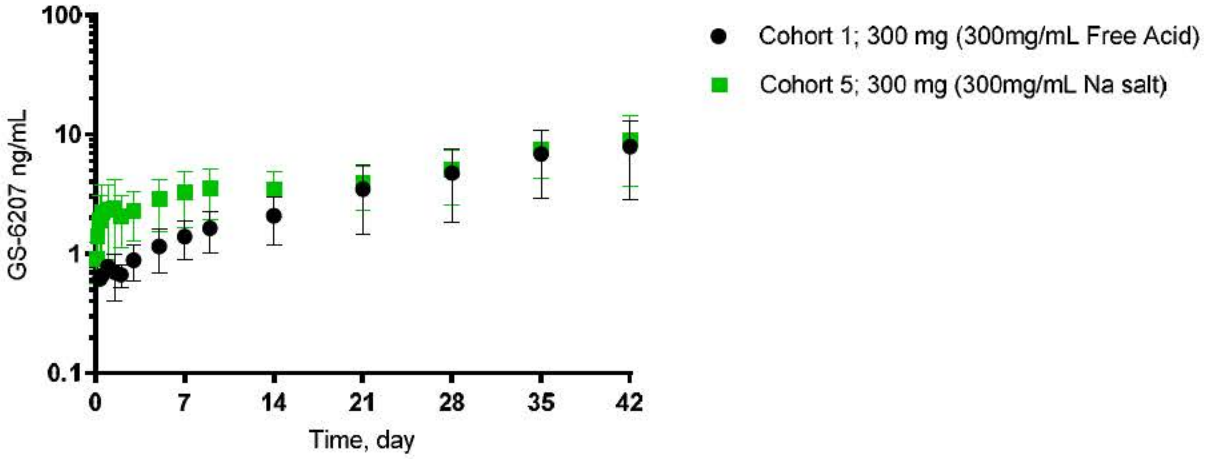
1.2.2.3. GS-US-200-4538 Summary

Study GS-US-200-4538 is an ongoing, Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single ascending doses of GS-6207 subcutaneous solution formulations. 40 unique subjects across 4 dosing cohorts have received either SC GS-6207 or placebo (4:1 ratio). Single SC doses of three formulations (300 mg/mL free acid; Cohort 1, 300 mg/mL Na salt; Cohort 5, and 150 mg/mL Na salt; Cohort 9) of GS-6207 have been administered at a 300 mg dose. Cohort 6 has received a 900 mg dose of 300 mg/mL Na salt. PK samples will be collected for up to 450 days. PK analysis is ongoing.

Preliminary PK profiles of GS-6207 after administration of single 300 mg SC doses of 300 mg/mL free acid (Cohort 1) and 300 mg/mL Na salt (Cohort 5) are presented in Figure 1-3 below. To date, there is insufficient data to calculate PK parameters from these solution formulations. Plasma concentrations of GS-6207 over the first 42 days were at least 5 fold lower than those following a 300 mg dose of the GS-6207 SC suspension evaluated in Study GS-US-200-4070 (Figure 1-1).

In a preliminary blinded review of safety data as of January 10, 2019 (n=20) no deaths, serious adverse events (SAEs), or Grade 3-4 adverse events (AEs) have been reported. Preliminary information provided by the investigator after 14 days of follow up indicates a favorable safety profile in subjects who received a 900 mg dose of GS-6207 in Cohort 6.

Figure 1-3. Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Subcutaneous Solutions of GS-6207 at 300 mg (N=8/cohort); 300 mg/mL Free Acid and 300 mg/mL Na Salt



1.2.2.4. GS-US-200-4072 Summary

Study GS-US-200-4072 is an ongoing, Phase 1b randomized, double-blinded, placebo-controlled, multi-cohort study of the safety, pharmacokinetics, and antiviral activity of GS-6207 administered as a subcutaneous injectable suspension in HIV-1 infected subjects conducted under IND 136260 (injectable). The primary objective of this study is to evaluate the short-term antiviral activity of GS-6207 compared to placebo GS-6207, with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are treatment-experienced but not currently taking ARV treatment. This study may enroll up to 40 subjects across 5 cohorts of 8 unique subjects per cohort.

All subjects will receive Biktarvy as a standard-of-care oral combination antiretroviral therapy immediately after completing the assessment of the primary endpoint (ie, Day 10) in order to minimize the risk of exposing subjects to GS-6207 monotherapy for an extended period of time. This study is currently enrolling.

In a preliminary blinded review of the available safety data as of February 26, 2019 when the first cohort had all completed Day 10 of GS-6207 150 mg, no deaths, serious adverse events (SAEs), or Grade 2-4 adverse events (AEs) have been reported. The preliminary safety data indicate a favorable safety profile in subjects with HIV-1 infection. Preliminary blinded HIV-1 RNA data showed a mean (range) 1.76 (1.49-2.06) log10 copies/mL decline in HIV-1 RNA at Day 10.

1.3. Tenofovir alafenamide (TAF)

Following its release from the prodrug TAF, TFV is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase that terminates the elongation of the viral DNA chain during the process of retroviral replication.

1.3.1. General Information

For further information on TAF, please refer to the investigator's brochure (IB). Information in the IB includes:

- Nonclinical pharmacology and toxicology
- Nonclinical pharmacokinetics (PK) and in vitro metabolism
- Preclinical pharmacology, pharmacokinetics, and toxicology
- Clinical experience

1.4. Rationale for this Study

Current oral combination ARV therapy can achieve and maintain virologic suppression in the majority of patients and even provide second or third line regimens after they fail their first line regimen for efficacy or safety reasons. However, there still remains a significant unmet medical need for heavily treatment experienced (TE) HIV patients, which can be met with an antiretroviral agent with a new mechanism of action. As there is no cross-resistance with agents in existing classes, such agents can be used in patients who develop resistance to agents in existing classes or in virologically suppressed patients without concern for losing certain classes altogether even if they develop resistance.

While current oral combination ARV therapy for the treatment of HIV-1 infection is efficacious and generally well tolerated, these agents need to be taken every day and require near-perfect adherence to achieve and maintain virologic suppression and minimize the emergence of drug-resistant variants. Given the potency of contemporary ART, a detectable viral load identified during chronic care for a patient with stable access to ART is most likely the result of poor adherence {The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents 2017}. As such, there remains a significant medical need for ARVs that can be administered less frequently (i.e., long-acting drug products) for all patients.

1.4.1. Rationale for the development of GS-6207

GS-6207 is a selective, multi-stage inhibitor of HIV-1 capsid function being developed as a novel therapeutic for the treatment of HIV-1 infection. GS-6207 is characterized by potent antiviral activity, a novel resistance profile, low predicted human clearance, low potential for drug-drug interactions, and low aqueous solubility. GS-6207 is anticipated to be active against all major types of HIV-1, including those that have developed resistance to existing classes of ARVs (eg, nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and integrase strand-transfer inhibitors [INSTIs]). This makes GS-6207 a useful antiretroviral agent for heavily treatment experienced patients with few options due to multiclass resistant HIV-1 infection. In addition, the physicochemical characteristics allow GS-6207 to be well suited for an extended-release parenteral formulation that can potentially be used as a novel long-acting antiretroviral (ARV) treatment administered monthly or less frequently.

To date, Gilead evaluated GS-6207 only in healthy volunteers and has not observed any safety signal of concern (see Section 1.2.2). The current study (GS-US-200-4072) is the first study of GS-6207 in humans with HIV-1 infection. This study will assess the safety, tolerability, PK, and antiviral activity of GS-6207 in treatment naïve or experienced but capsid inhibitor (CAI) and integrase strand transfer inhibitor (INSTI) naive. The study involves 10 days of monotherapy that will allow for the assessment of antiviral activity over a range of GS-6207 exposures in HIV-1 infected subjects. The study will also allow for the evaluation of the safety and PK of GS-6207 in HIV-1 infected subjects. The data from this study will support dose selection for Phase 2 and 3 studies.

1.4.2. Rationale for the development of weekly oral TAF

TAF is a next generation oral prodrug of TFV that, compared to TDF, delivers increased intracellular levels of TFV-DP, in conjunction with lower systemic TFV exposure. TAF provides enhanced delivery of TFV to peripheral blood mononuclear cells (PBMCs), lymphatic organs, and hepatocytes, resulting in higher intracellular levels of the active phosphorylated moiety TFV-DP, more effective suppression of residual viral replication in a wider range of reservoir and anatomic sanctuaries of HIV, and lower systemic circulating levels of TFV, resulting in a better overall profile.

The combination of low circulating TFV and high intracellular TFV-DP (as compared with TDF) raises the prospect that less frequent administration of higher dose TAF may be a safe and effective alternative for patients for whom daily adherence is challenging.

While current oral combination ARV therapy for the treatment of HIV-1 infection is efficacious and generally well tolerated, these agents need to be taken every day and require near-perfect adherence to achieve and maintain virologic suppression and minimize the emergence of drug-resistant variants. Given the potency of contemporary ART, a detectable viral load identified during chronic care for a patient with stable access to ART is most likely the result of poor adherence {The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents 2017}. As such, there remains a significant medical need for ARVs that can be administered less frequently (i.e., long-acting drug products) for all patients. An oral ARV which could be administered weekly might offer the potential for improved treatment for some patients. If so, viral suppression for 10 days after a single dose can support a weekly administration.

1.5. Rationale for the Dose Selection

1.5.1. GS-6207

Selection of the GS-6207 SC suspension doses for this study takes into consideration the available safety, tolerability and PK data for SC GS-6207 from the ongoing SC single ascending dose study in healthy volunteers (GS-US-200-4070), as well as preliminary safety and antiviral activity data in this study following administration of GS-6207 150 mg to HIV-1 infected subjects (GS-US-200-4072).

As of February 1, 2019, 40 subjects (32 active and 8 placebo) have received a single dose of GS-6207 via subcutaneous injection (SC 30 to 450 mg). All subjects have completed at least 168 days of follow up or discontinued the study. In the blinded review of safety data, GS-6207 was generally well-tolerated. There have been no deaths, serious adverse events (SAEs), or Grade 3-4 adverse events (AEs) reported. Injection site reactions occurred in 21 of 40 subjects (53%) these included injection site erythema (15 subjects, 38%), injection site pain (14 subjects, 35%), injection site nodules (9 subjects, 23%), injection site induration (8 subjects, 20%), and injection site swelling (7 subjects, 18%). The only other AE that was reported by more than 10% of subjects was headache (5/40, 13%).

GS-6207 PK was shown to be dose proportional across the dose range of 30 to 450 mg in Study GS-US-200-4070. Based on the PK data from Study GS-US-200-4070, GS-6207 150 mg is expected to result in a GS-6207 concentration at Day 10 (C_t) that is 4-fold higher than the protein adjusted EC_{95} against wild type HIV virus ($paEC_{95}$; 3.8 ng/mL), and was selected for evaluation in Cohort 1 (Table 1-1) of this study. PK analysis is ongoing. Preliminary blinded data from Cohort 1 demonstrated a favorable safety profile and a mean decrease of 1.76 log10 copies/mL in HIV-1 RNA at Day 10 following administration of 150 mg GS-6207. Based on these data, a dose of 50 mg and 450 mg have been selected for Cohorts 2 and 3, respectively. Doses of 20 mg and 750 mg were subsequently selected for Cohorts 4 and 5 respectively.

1.5.2. TAF

The PK, safety and efficacy of TAF have been comprehensively characterized across several TAF-containing clinical development programs including in combination with B/F/TAF used in this study. The results of clinical studies, including the proof-of-concept TAF monotherapy evaluation in HIV-infected subjects, informed selection of TAF oral doses for this study.

Briefly, Phase 1 studies demonstrated a favorable safety profile and approximately dose proportional increases in exposure for TAF, TFV and TFV-DP (active intracellular metabolite) across the dose range of 8 to 125 mg. In Phase 3 clinical studies, TAF 25 mg exhibited a favorable safety profile when dosed in subjects with chronic hepatitis B infection (CHB) or in combination with other ARV agents for the treatment of HIV.

The results from the two TAF proof-of-concept short-term (10-14 day) monotherapy studies in treatment-naïve HIV-1 subjects showed dose-dependent mean reductions in HIV-1 RNA of 0.99, 1.43, 1.52 $\log_{10}$ copies/mL on Day 10 at TAF doses of 8 mg, 25 mg, 40 mg QD, respectively, and a mean decrease of 1.48 $\log_{10}$ copies/mL on Day 10 at TAF 120 mg QD (GS-US-120-0104 and GS-US-120-1101) {Ruane 2013}. Based on these data, a single dose of TAF 200 mg was chosen for the initial evaluation in this study (Part B, Cohort 6). Assuming dose proportionality, TAF 200 mg is predicted to provide intracellular exposure of the active metabolite, TFV-DP, at Day 10 similar to that observed following daily dosing of 25 mg TAF; and as such achieve comparable viral load reduction through Day 10.

TAF doses to be evaluated in adaptive cohorts 7 and 8 (up to 600 mg single dose) will be selected based on cumulative safety, antiviral activity and available pharmacokinetic data from previous cohorts in Part B. These doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses. Following administration of 600 mg TAF, predicted TFV C_{max} (236 ng/mL) is projected to be similar to predicted average daily TFV exposures (1033 ng/mL) and up to 50% lower, respectively, than that observed following daily administration of TDF 300 mg (C_{max}: 300 ng/mL and average daily exposure: 2290 ng/mL); accordingly, doses of up to 600 mg TAF are supported by clinical safety data from the TDF 300 mg development program {STRIBILD® 2019, VIREAD 2019}.

The proposed dose range allows for sufficient dose-separation between cohorts for examining safety, antiviral activity and pharmacokinetics of a single dose of oral TAF, and maximizes the probability of observing a dose/exposure -response relationship. Since there are sufficient subjects in the placebo group from Part A, and the safety of TAF >125 mg is unknown, all subjects in Part B will be enrolled to receive TAF.

1.6. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown adverse events (AEs), including injection site reaction, general risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of multiple phlebotomies. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for monitoring of AEs will be well defined and closely followed.

In addition, potential risks to HIV positive subjects include prolonged exposure (weeks to months) to subtherapeutic concentrations of GS-6207, which can lead to HIV-1 developing resistance to GS-6207. Strategies to mitigate these risks include initiation of B/F/TAF, which is an FDA-approved single tablet regimen with established efficacy and safety profile, on Day 10. With the initiation of B/F/TAF most subjects are expected to achieve virologic suppression within a few weeks, which substantially reduces the risk of HIV-1 developing resistance. Similarly, subjects receiving TAF monotherapy have a risk of developing TAF resistance. However, TAF has a shorter half-life than GS-6207 and the same mitigation strategy of initiation of B/F/TAF at Day 10 will be used.

There is no direct benefit to subjects participating in this study; however, data from this study will support the development of GS-6207 and weekly TAF for the treatment of HIV-1 infection. Potential benefits may include the participant's contribution to understanding the antiviral activity, safety, tolerability, and pharmacokinetics of GS-6207 (Part A) or TAF (Part B) (i.e. how much GS-6207 or TAF gets into the blood stream).

Given the above, the benefit-risk balance for this study is considered positive.

1.7. Compliance

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

2. OBJECTIVES

Part A (Cohorts 1 – 5)

The primary objective of this study is as follows:

- To evaluate the short-term antiviral activity of GS-6207 compared to placebo GS-6207, with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but capsid inhibitor (CAI) naïve.

The secondary objectives of this study are as follows:

- To investigate the safety and tolerability of GS-6207 as compared to placebo GS-6207 in HIV-1 infected subjects
- To characterize the plasma pharmacokinetics (PK) of GS-6207 in HIV-1 infected subjects
- To characterize the PK/pharmacodynamics of GS-6207 concentration and viral dynamics of HIV-1.
- To determine the number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 at each dose level
- To examine any emergence of capsid inhibitor (CAI) resistance

Part B (Cohorts 6 – 8)

The primary objective of this study is as follows:

- To evaluate the short-term antiviral activity of TAF with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but without resistance to TAF.

The secondary objectives of this study are as follows:

- To investigate the safety and tolerability of TAF in HIV-1 infected subjects
- To characterize the pharmacokinetics (PK) of TAF and its metabolites in HIV-1 infected subjects
- To examine any emergence of TAF resistance.

CCI [redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint is the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10.

Secondary endpoints include:

- Incidences of adverse events and graded laboratory abnormalities
- PK parameters of GS-6207 (Part A) and TAF (and its metabolites, as appropriate) (Part B)
- Correlation between C_t (concentration at Day 10) of GS-6207 (Part A) and the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10
- Number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 (Part A)
- Incidences of any emergence of CAI resistance (Part A)
- Incidences of any emergence of TAF resistance (Part B)

3.2. Study Design

Randomized, double-blinded, placebo-controlled, multi-cohort study of GS-6207 (Part A) and single-arm study of TAF (Part B) monotherapy in subjects with HIV-1 infection

3.3. Study Treatments

This study may enroll up to 5 cohorts in Part A and up to 3 cohorts in Part B, of approximately 8 unique subjects per cohort. All subjects will be enrolled after the completion of screening procedures and following confirmation of study eligibility. Within each Cohort (n=8) in Part A, subjects will be randomized in a 3:1 ratio to receive active GS-6207 (n=6) or placebo (n=2). Within each Cohort (n=8) in Part B, subjects will be enrolled to receive active oral TAF.

Part A: A single dose of GS-6207 or placebo will be administered subcutaneously (SC) in the abdomen on Day 1. GS-6207 doses may be administered as multiple SC injections at different abdominal sites, as appropriate. In the case where multiple injections are administered for a given dose, the first and last injections should be no more than 30 minutes apart. If necessary for practical reasons, the period may be extended up to 45 minutes.

Cohort	*Treatment*
1	*150 mg GS-6207*
2	*50 mg GS-6207*
3	*450 mg GS-6207*
4	*20 mg GS-6207*
5	*750 mg GS-6207*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety and PK data.

The doses to be evaluated in Cohorts 2 through 5 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts as well as available safety (through at least Day 14) and pharmacokinetic data from Study GS-US-200-4070 (Phase 1, first-in-human, single ascending dose study of GS-6207 SC suspension formulation). Cohorts 2-5 may be initiated in parallel. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses either in this study or in Study GS-US-200-4070; the same SC suspension formulation is being administered in both studies. The highest proposed dose in this study, GS-6207 900 mg, represents a 2-fold dose escalation over GS-6207 450 mg, which has been shown to be safe and well tolerated in Study GS-US-200-4070, based on a blinded review of safety data.

Observed study drug dosing is required at Day 1.

Part B: A single dose of TAF will be administered orally on Day 1.

Cohort	*Treatment*
6	*200 mg TAF*
7	*Up to 600 mg TAF*
8	*Up to 600 mg TAF*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety and PK data.

The doses to be evaluated in Cohorts 7-8 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses in this study. Cohorts 7 and 8 may be run in parallel.

Observed TAF dosing is required at Day 1.

3.4. Duration of Treatment

Regardless of Cohort in this study, the procedures are identical. Following screening and Day 1 visits, subjects will be required to visit the clinic on Days 2, 3, 4, 5 (Part B only, if possible), 6 (Part B only, if possible), 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225.

All subjects will be dosed with either active GS-6207 or placebo (Part A) or TAF (Part B) on Day 1.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 64 subjects who meet all the eligibility criteria will be enrolled.

Replacement subjects may be enrolled for subjects who do not complete all procedures for reasons other than discontinuation due to monotherapy treatment related adverse events.

4.2. Inclusion Criteria (Parts A and B)

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

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

2) Must be between 18 and 65 years of age, inclusive on the date of the screening visit

3) **Cohorts 1 - 5:** Antiretroviral treatment naïve OR experienced but capsid inhibitor (CAI) and integrase strand transfer inhibitor (INSTI) naïve and have not received any anti-HIV treatment, including antiretroviral medications received for prevention (PrEP) or post exposure prophylaxis (PEP), within 12 weeks prior to screening

   Cohorts 6 - 8: Antiretroviral treatment naïve OR experienced but integrase strand transfer inhibitor (INSTI) naïve and have not received any anti-HIV treatment, including antiretroviral medications received for prevention (PrEP) or post exposure prophylaxis (PEP), within 12 weeks prior to screening

4) Plasma HIV-1 RNA $\geq$ 5,000 copies/mL but $\leq$ 400,000 copies/mL

5) CD4+ cell count > 200 cells/mm^3

6) **Cohorts 1 - 5:** Screening HIV-1 capsid genotypic report provided by Gilead must not show any mutation known to be associated with in vitro resistance to GS-6207 (L56I, M66I, Q67H, Q67Y, K70N, N74D, N74S, A105E, or T107N in HIV-1 capsid)

   Cohorts 6 - 8: HIV-1 capsid genotyping criteria do not apply

7) Must be willing to initiate B/F/TAF on Day 10

8) Screening genotype report provided by Gilead must show genotypic sensitivity to the components of B/F/TAF at Screening to allow its initiation on Day 10

9) No documented or suspected resistance to the components of B/F/TAF to allow its initiation on Day 10

10) Screening genotype report provided by Gilead must show genotypic sensitivity to at least one agent in the non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI) classes such that a viable standard-of-care ARV regimen can be constructed in the future

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

12) Adequate renal function:

Estimated glomerular filtration rate ≥ 70 mL/min according to the Cockcroft-Gault formula {Cockcroft 1976}:

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

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

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

14) Alkaline phosphatase ≤ ULN

15) Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin

16) Adequate hematologic function (absolute neutrophil count ≥ 750/mm^3; platelets ≥ 50,000/mm^3; hemoglobin ≥ 8.5 g/dL) (Those with chronic neutropenia with no clinical significance can enroll at the discretion of the investigator.)

17) Females of childbearing potential (as defined in Appendix 6 for Cohorts 1 - 5, and Appendix 7 for Cohorts 6 - 8) must have a negative serum pregnancy test at screening.

18) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol specified method(s) of contraception as described in Appendix 6 for Cohorts 1 - 5, and Appendix 7 for Cohorts 6 - 8.

19) Female subjects must refrain from egg donation and in vitro fertilization during treatment and until at least:

- 300 days following the dose of study drug, for Cohorts 1 – 5
- 7 days following the last dose of Biktarvy on the study, for Cohorts 6 – 8

20) **Cohorts 1 - 5:** Male subjects must refrain from sperm donation during treatment and until at least 360 days following the dose of study drug.

Cohorts 6 - 8: Male subjects must refrain from sperm donation during treatment on the study.

4.3. Exclusion Criteria (Parts A and B)

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

1) Anticipated to start HIV-1 therapy between Days 1 and 9

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

3) Recent use of any approved or investigational antiretroviral drugs within 12 weeks prior to screening

4) Have taken any prescription medications or over-the-counter medications, including herbal products, within 42 days prior to start of study drug dosing without prior approval form the sponsor, with the exception of vitamins and/or acetaminophen and/or hormonal contraceptive medications

5) Known hypersensitivity to the study drug, the metabolites or formulation excipients, or to B/F/TAF

6) A new AIDS-defining condition diagnosed within the 30 days prior to screening (refer to Appendix 5)

7) Hepatitis C virus (HCV) antibody positive and HCV RNA detectable

8) Chronic Hepatitis B Virus (HBV) infection, as determined by either:

   - Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit

   - Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit.

9) Pregnant or lactating females

10) Have an implanted defibrillator or pacemaker

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

12) A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS are eligible, but must not have received any systemic therapy for KS within 42 days of Day 1 and must not be anticipated to require systemic therapy during the study

13) Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 42 days prior to Day 1

5. INVESTIGATIONAL MEDICINAL PRODUCT AND B/F/TAF

5.1. Randomization, Blinding and Treatment Codes

Part A

Subjects will be assigned a screening number at the time of consent. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment.

Following completion of screening procedures, eligible subjects will be randomized in a 3:1 ratio within each cohort to receive either GS-6207 (n=6) or placebo (n=2) on Day 1, and assigned a subject number.

All screening tests and procedures must be completed and reviewed by the investigator prior to the administration of the study drug on Day 1. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from Sponsor. A new unique subject number will be assigned to the replacement subject.

The study pharmacist, or designee will remain unblinded throughout the study to prepare the study drug. The designated site staff administering the study drug will also remain unblinded. For additional information on maintaining the study blind, please refer to the study Pharmacy Manual. The Pharmacokinetics File Administrator, or designee, who facilitates data transfer of PK files between Gilead and vendors, will remain unblinded.

Part B

Subjects will be assigned a screening number at the time of consent. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment.

Following completion of screening procedures, eligible subjects will be enrolled to receive TAF and will be assigned a subject number.

All screening tests and procedures must be completed and reviewed by the investigator prior to the administration of the study drug on Day 1. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from Sponsor. A new unique subject number will be assigned to the replacement subject.

5.1.1. Procedures for Breaking Treatment Codes (Part A)

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless

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

All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

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

5.2. Description and Handling GS-6207, TAF and B/F/TAF

5.2.1. Formulation

5.2.1.1. GS-6207 and Placebo

GS-6207 injectable suspension, 100 mg/mL is a sterile, preservative-free, white to off-white to tan suspension for subcutaneous injection. In addition to the active ingredient, the suspension contains the following inactive ingredients: poloxamer 188, sodium chloride, phosphate buffer, and water for injection.

The placebo is a sterile, clear, colorless solution for subcutaneous injection. The solution contains the following inactive ingredients: poloxamer 188, sodium chloride, phosphate buffer, and water for injection.

5.2.1.2. TAF

TAF tablets, 25 mg, are yellow, round, film-coated tablets debossed with "GSI" on one side of the tablet and "25" on the other side of the tablet. In addition to the active ingredient, the tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

5.2.1.3. Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF, 50/200/25 mg)

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

5.2.2. Packaging and Labeling

5.2.2.1. GS-6207 and Placebo

GS-6207 injectable suspension, 100 mg/mL, and placebo solution are each filled into a 3 mL borosilicate glass vial and closed with a rubber stopper and aluminum seal with a polypropylene flip-off cap. Each single use vial contains sufficient volume (1.2 mL) to allow withdrawal of 1 mL of GS-6207 injectable suspension or placebo solution.

The vials are labeled and placed into secondary packaging for storage.

Study drug to be distributed to centers in the US shall be labeled to meet requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.2.2.2. TAF

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

Study drug to be distributed to centers in the US shall be labeled to meet requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.2.2.3. Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF, 50/200/25 mg)

Bictegravir /Emtricitabine /Tenofovir Alafenamide (B/F/TAF, 50/200/25 mg) is packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

5.2.3.1. GS-6207 and Placebo

GS-6207 100 mg/mL injectable suspension and placebo solution vials should be stored refrigerated at 2 °C to 8 °C (36 °F to 46 °F). Storage conditions are specified on the label. Until dispensed for dosing, all vials of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the sterility, stability, and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.2.3.2. TAF

TAF tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.2.3.3. Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF, 50/200/25 mg)

Bictegravir /Emtricitabine /Tenofovir Alafenamide (B/F/TAF, 50/200/25 mg) stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of B/F/TAF should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, B/F/TAF should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.3. Dosage and Administration of GS-6207 (Part A, Cohorts 1 - 5)

Part A of this study may enroll up to 5 cohorts of approximately 8 unique subjects per cohort. All subjects will be enrolled after the completion of screening procedures and following confirmation of study eligibility. Within each Cohort (n=8) in Part A, subjects will be randomized in a 3:1 ratio to receive active GS-6207 (n=6) or placebo (n=2).

A single dose of GS-6207 or placebo will be administered subcutaneously (SC) in the abdomen on Day 1. GS-6207 doses may be administered as multiple SC injections at different abdominal sites, as appropriate. In the case where multiple injections are administered for a given dose, the first and last injections should be no more than 30 minutes apart. If necessary for practical reasons, the period may be extended up to 45 minutes.

Cohort	***Treatment***
1	*150 mg GS-6207 or placebo*
2	*50 mg GS-6207 or placebo*
3	*450 mg GS-6207 or placebo*
4	*20 mg GS-6207 or placebo*
5	*750 mg GS-6207 or placebo*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety data.

The doses to be evaluated in Cohorts 2 through 5 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts as well as available safety (through at least Day 14) and pharmacokinetic data from Study GS-US-200-4070 (Phase 1, first-in-human, single ascending dose study of GS-6207 SC suspension formulation). Cohorts 2-5 may be initiated in parallel. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses either in this study or in Study GS-US-200-4070; the same SC suspension formulation is being administered in both studies. The highest proposed dose in this study, GS-6207 900 mg, represents a 2-fold dose escalation over GS-6207 450 mg, which has been shown to be safe and well tolerated in Study GS-US-200-4070, based on a blinded review of safety data.

5.4. Dosage and Administration of TAF (Part B, Cohorts 6 - 8)

Part B of this study may enroll up to 3 cohorts of approximately 8 unique subjects per cohort. All subjects will be enrolled after the completion of screening procedures and following confirmation of study eligibility. Within each Cohort (n=8) in Part B, subjects will be enrolled to receive active oral TAF.

A single dose of TAF will be administered orally on Day 1.

Cohort	***Treatment***
6	*200 mg TAF*
7	*Up to 600 mg TAF*
8	*Up to 600 mg TAF*

The Sponsor may elect to hold dosing, or stop study enrollment at any time based on review of preliminary safety and PK data.

The doses to be evaluated in Cohorts 7-8 will be determined based on cumulative safety (through at least Day 14), available PK and viral kinetic data from previous cohorts. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses in this study. Cohorts 7 and 8 may be run in parallel.

Observed TAF dosing is required at Day 1.

5.5. Prior and Concomitant Medications

The following medications are excluded while subjects are participating in **Part A**:

- Any prescription medications and over-the-counter medications, including herbal products, with the exception of vitamins, and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications. However, the short-term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation due to ECG leads will be allowed. If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor and if approved, subjects may continue to participate in the study.
- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.

For Part A, if a subject discontinues B/F/TAF between the Day 10 and Day 225 visits, they can switch to an alternative ARV regimen, which should not contain the following prohibited ARVs:

Prohibited ARVs	HIV Protease Inhibitors
	RTV or COBI containing regimens
	Efavirenz
	Etravirine
	Nevirapine

The following medications are excluded while subjects are participating in **Part B**:

- TAF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters {DESCOVY® 2017}. Drugs that inhibit or induce Pgp or BCRP activity may lead to increases or decreases, respectively, in TAF absorption. In vitro data suggest TAF may inhibit or induce CYP3A at doses up to 600 mg, however, given its short half-life and transient exposure, clinically relevant changes in CYP3A substrates are not expected following co-administration with a single dose TAF.
- Medications that are potent inhibitors or inducers of Pgp/BCRP are prohibited, and use of herbal/natural supplements are excluded while subjects are participating in this study. Table 5-1 contains examples of medications that are to be excluded while subjects are participating in the study in Part B. As this table is not exhaustive, all concomitant medications are to be reviewed with the sponsor until Day 10. After Day 10, the investigator should follow the current USPI for B/F/TAF {BIKTARVY® 2018}.
- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician, are prohibited.

Table 5-1. List of medications that are prohibited due to the potential for drug-drug interaction with TAF

Medication Class	Disallowed Medications
Anti-arrhythmics	Amiodarone, Dronedarone, Propafenone
Anti-anginal agents	Ranolazine
Anti-biotics	Clarithromycin
Anti-convulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Anti-fungals	Itraconazole
Anti-malarials	Quinidine
Anti-mycobacterials	Rifapentine, Rifabutin, Rifampin
Anti-retroviral agents	Any antiretroviral drug that is not part of the study regimen
Beta blockers	Carvedilol
Ca channel blockers	Verapamil
Herbal/Natural Supplements	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)

5.6. Dispensing, Accountability, and Disposal or Return of GS-6207 and TAF (study drugs) and B/F/TAF

The investigator (or designee, eg, study center pharmacist) will acknowledge receipt of the study drugs and B/F/TAF (after reviewing the shipment's content and condition) from Gilead (or designee). The investigator will maintain an accurate inventory of all study drug and B/F/TAF. The study drug will be administered at the study center by qualified study center staff. The dose of study drug administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the study center), which indicates the date and quantity of each dosage formulation dispensed to individual subjects.

Where possible, study drug and B/F/TAF should be destroyed at the site. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies and B/F/TAF. The study monitor will provide instructions for return.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead , the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug or B/F/TAF is destroyed on site, the investigator must maintain accurate records for all drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the drugs. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead. Refer to the Pharmacy Binder for study drug disposal/return instructions. The study monitor will review study drug supplies and associated records at periodic intervals.

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 and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total trial enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or trial-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 42 days prior to 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 42 days of the screening visit
- 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)
- 12-lead ECG performed supine
- Height and Weight
- Obtain blood and urine samples as described in Section 6.6
- Review of AEs and concomitant medications

Once eligibility is confirmed, each subject will be assigned a unique subject number. Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. Prior to or during the Day 1 visit in **Part A** the Investigator or designee will enroll the subject using the Interactive Web Response System (IWRS). In **Part B**, the Investigator will contact Gilead Sciences to obtain the subject number. The subject number assignment may be performed up to 7 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 42 days after screening for Day 1 assessments. **Subjects will be instructed to fast overnight (≥ 6 hours) prior to the Day 1 visit.**

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

Subjects will be required to visit the clinic on Days 1, 2, 3, 4, 5 (Part B only, if possible), 6 (Part B only, if possible), 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225.

Subjects will be required to fast overnight (≥ 6 hours) prior to visit on Days 1, 3, 7, 10, 85, 169, and 225 for laboratory analyses.

6.3.1. Day 1

The following procedures are to be completed at the Day 1 visit prior to study drug dosing.

- 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)
- Weight
- 12-lead ECG performed supine (pre-dose)
- Obtain blood and urine samples as described in Section 6.6 (Note: all blood and urine samples should be collected pre-dose on Day 1, except for PK samples as noted in Section 6.6)
- **Part B:** A single dose of TAF will be administered orally on Day 1 at the study center under fasted conditions, with 240 mL of water following an overnight fast (no food or drink, except water, for at least 6 hours).

  On Day 1, subjects will be restricted from food intake until after collection of the 4-hour blood draw. Additionally, subjects will be restricted from water consumption 1 hour before and 2 hours after dosing, except for the 240 mL of water given with the study drug. Subjects will fast until 2 hours after study drug administration. Water may be freely consumed following the 2-hour blood draw and for the remainder of the collection period. Subjects may eat after the 4 hour post-dose blood draw.

6.3.2. Assessments on Days 2, 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225

Subjects will be required to fast overnight (≥ 6 hours) prior to visit on Days 3, 7, 10, 85, 169 and 225 for laboratory analyses. Study visit Days 29, 43, 57, 85, 113, 141, 169 and 197 may be completed within ± 2 days of the protocol-specified visit date.

The following procedures are to be completed at all visits unless otherwise specified:

- Review of AEs and changes in concomitant medications
- Symptom directed physical examination
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- 12-lead ECG performed supine (Days 2, 10, 29, 57, 85, 169 and 225)
- Obtain blood and urine samples as described in Section 6.6
- All subjects will initiate B/F/TAF on Day 10 after completion of all assessments.
  - B/F/TAF will be dispensed at Days 10, 43, 85, 141 and 197.

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6.4. Early Study Discontinuation Assessments

If a subject discontinues their participation prior to Day 225, Early Termination Visit should be performed.

However, if there are any abnormal laboratory results indicating that there is a possible or probable causal relationship with the study drug, every attempt should be made to keep the subject in the study and repeat those laboratory tests weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

The following evaluations should be performed at the Early Termination 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)
- Weight
- Obtain blood and urine samples as described in Section 6.6
- Counsel subject regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility

6.5. Criteria for Discontinuation of Study

Study 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
- Subject request to discontinue for any reason
- Subject noncompliance with B/F/TAF
- Pregnancy during the study; refer to Appendix 6 and Appendix 7
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.6. Clinical Laboratory Assessments

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

6.6.1. Blood Samples

- Blood sample collection for the following laboratory analyses will be performed at every visit, unless specified:

  — Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be randomized **(Screening and Days 29, 57, 85, 113, 141, 169, 197 and 225)**

  — Serum FSH test (required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure) **(Screening only)**

  — Urine pregnancy test (females of childbearing potential only). If the test is positive, confirmatory serum test should be sent and study drug dosing should be delayed until results obtained **(Day 1)**

  — Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) **(All visits <u>except</u> Days 2, 4, 8 and 9).** Subjects will be required to fast overnight (≥ 6 hours) prior to visit on Days 3, 7, 10, 85, 169 and 225.

  — Estimated glomerular filtration rate according to the Cockcroft-Gault formula for Creatinine clearance **(All visits <u>except</u> Days 2, 4, 8 and 9)**

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

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

  — Hematology profile: complete blood count (CBC) with differential and platelet count **(All visits <u>except</u> Days 2, 4, 8 and 9)**

  — CD4+ cell count **(Screening and Days 1, 10, 29, 43, 57, 85, 113, 141, 169, 197 and 225)**

  — Plasma HIV-1 RNA. Any subsequent HIV-1 genotype and phenotype testing will be performed as described in Section 6.7.

  — HIV-1 genotype and phenotype for PR, RT, IN, and capsid **(Screening only)**

  — HIV-1 capsid genotype and phenotype **(Day 10)**

  — HIV DNA genotyping **(Days 85, 169 and 225)**

— Hepatitis B virus (HBV) serologies (HBV surface antigen, HBV core antibody, HBV surface antibody) **(Screening only)**

— Hepatitis C virus (HCVAb) serology **(Screening only)**

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— Plasma storage samples for safety and virology testing (HIV-1 capsid genotype and phenotype) **(Not collected at Screening visit)**

GS-6207 PK Sampling (Part A, Cohorts 1 – 5)

— Blood samples to determine PK in plasma:

- The exact time of study drug administration and the exact time points (date and 24-hour clock) of collection of plasma samples must be carefully recorded.
- **Day 1:** Time 0 (pre-dose), 1, 2, 4, 8, 12 and 24 hours post dose (relative to study drug dosing time) blood sample collection to determine pharmacokinetics (PK) in plasma on Day 1
- **Days 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197 and 225**: a single anytime PK sample will be collected.

TAF PK sampling (Part B, Cohorts 6 - 8):

— Plasma PK samples will be collected to determine PK of TAF and its metabolite, TFV, at the following time points relative to study drug dosing:

- **Day 1:** 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours post dose.
- **Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10** at approximately the same time in the morning as pre-dose on Day 1.

— PBMC PK samples will be collected to determine PK of TFV-DP at the following time points relative to study drug dosing:

- **Day 1:** 0 (pre-dose), 1, 2, 4, 6, 8, 12, 24 and 48 hours post dose.
- **Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10** at approximately the same time in the morning as pre-dose on Day 1.

6.6.2. Urine Samples

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

- Urinalysis and urine Chemistry: including color & clarity, specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase and microscopic (if microscopic elements are seen), urine protein, albumin, creatinine, phosphate, calcium, magnesium and uric acid **(All visits except Days 2, 4, 8 and 9)**

- Urine pregnancy test (females of childbearing potential only). If the test is positive, confirmatory serum test should be sent and study drug dosing should be delayed until results obtained **(Day 1)**

- Urine storage **(All visits except Screening, Days 2, 4, 8 and 9)**

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6.7. Management of Virologic Failure after Initiation of B/F/TAF on Day 10

Subjects who experience either suboptimal virologic response (SVR) or virologic rebound (VR) after initiating B/F/TAF, as defined below, will be considered to have virologic failure.

6.7.1. Suboptimal Virologic Response (SVR)

- HIV-1 RNA $\geq$ 50 copies/mL **and** less than 1 $\log_{10}$ HIV-1 RNA reduction from Day 10 at the Day 57 visit

Following the first instance of SVR at Day 57, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after first SVR visit) for confirmation of SVR. A plasma sample from either the first instance or the SVR confirmation visit will be tested for HIV-1 capsid genotypic and phenotypic resistance. In addition, if SVR is confirmed, a plasma sample from the SVR confirmation visit will be tested for HIV-1 PR, RT, and IN genotypic and phenotypic resistance.

6.7.2. Virologic Rebound (VR)

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

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

At any visit after achieving HIV-1 RNA < 50 copies/mL, if the HIV-1 RNA is ≥ 50 and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples, if available. If the repeat result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA VR) for confirmation of VR.

A plasma sample from either the first instance or the VR confirmation visit will be tested for HIV-1 capsid genotypic and phenotypic resistance. In addition, if VR is confirmed, a plasma sample from the VR confirmation visit will be tested for HIV-1 PR, RT, and IN genotypic and phenotypic resistance.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7)
- 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 eCRF.

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

The distinction between the seriousness and the severity of an adverse event should be noted.

Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

7.3. 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 administration of study drug, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following administration of study drug, all AEs, regardless of cause or relationship, that occur on or before the last posttreatment follow-up visit, or in the case of early termination, 225 days after the administration of study drug must be reported to the eCRF database as instructed.

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

Serious Adverse Events

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

Any SAEs and deaths that occur on or before the last post-treatment follow-up visit, or in the case of early termination, 225 days after the administration of study drug, regardless of causality, should also be reported.

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

Gilead PVE contact information: Email: PPD
Fax: PPD

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

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

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

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

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

Standard of Care Adverse Event Reporting

This is a study in which B/F/TAF will be administered as standard of care treatment for HIV. Investigators are encouraged to report any special situations, including pregnancy, and adverse events associated with B/F/TAF or any other commercially available Gilead product administered as part of standard-of-care treatment to Gilead PVE.

Gilead PVE contact information: Email: PPD
Fax: PPD

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

Laboratory abnormalities without clinical significance are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urine chemistry) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational study discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, 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 (ie, anemia), not the laboratory result (ie, decreased hemoglobin).

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

7.6. Toxicity Management

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

- Clinical events and clinically significant laboratory abnormalities will be graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).
- Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically as clinically indicated, until symptoms subside, and until 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.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results, unless such a delay is not consistent with good medical practice.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, 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 with an AE is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.1.2. 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 the pregnancy. The outcome should be reported to or Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email 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 Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Part A (Cohorts 1 – 5):

The primary analysis objective of this study is to evaluate the short-term antiviral activity of GS-6207 compared to placebo administered subcutaneously (SC) in the abdomen on Day 1, with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but capsid inhibitor (CAI) naïve.

The secondary analysis objectives of this study are to investigate the safety and tolerability of GS-6207 as compared to placebo, to characterize the plasma pharmacokinetic (PK) of GS-6207 and the PK/pharmacodynamic (PD) (or dose-response) relationship between GS-6207 concentration at Day 10 and the viral dynamics of HIV-1, to determine the number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10, and to examine any emergence of CAI resistance.

Part B (Cohorts 6 - 8):

The primary analysis objective of this study is to evaluate the short-term antiviral activity of a single dose of oral TAF with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve or are experienced but without resistance to TAF.

The secondary analysis objectives of this study are to investigate the safety and tolerability of TAF, to characterize the PK of TAF, and to examine any emergence of TAF resistance.

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8.1.2. Primary Endpoint

The primary endpoint is the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10.

8.1.3. Secondary Endpoint

Secondary endpoints include:

- Incidences of adverse events and graded laboratory abnormalities
- PK parameters of GS-6207 (Part A) and TAF (and its metabolites, as appropriate) (Part B)
- Correlation between C_t (concentration at Day 10) of GS-6207 (Part A) and the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from baseline through Day 10
- Number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 (Part A)
- Incidences of any emergence of CAI resistance (Part A)
- Incidences of any emergence of TAF resistance (Part B)

8.1.4. Other Endpoints of Interest

The correlation between AUC of TAF, and its metabolites, as appropriate, and the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from baseline through Day 10.

8.2. Analysis Conventions

8.2.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. The assignment of subjects to analysis sets will be done before the study blind is broken for analysis.

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as full analysis set (FAS), which includes all subjects who are randomized and receive full dose of randomized study drug. Subjects with major eligibility violations that are identifiable based on pre-randomization characteristics may be excluded. Subjects will be grouped according to the treatment to which they are randomized.

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as safety analysis set, which includes all subjects who are randomized and receive any dose of study drug. Subjects who receive treatment other than that intended will be analyzed according to treatment received.

8.2.1.3. Pharmacokinetics

The primary analysis set for PK analyses is defined as GS-6207 or TAF PK analysis set, which includes all subjects who are randomized, receive any dose of GS-6207 or TAF, and have at least 1 nonmissing post baseline concentration value for GS-6207 or TAF, or its metabolites.

8.2.1.4. Pharmacokinetic/Pharmacodynamic Analysis Set

The PK/PD analysis set includes all subjects who are in full analysis set and have both nonmissing C_t of GS-6207 and the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10.

8.3. Data Handling Conventions

Logarithm (base 10) transformation will be applied to HIV-1 RNA levels for efficacy analysis. Natural logarithm transformation for all PK parameters of GS-6207, TAF, and its metabolites (eg, C_{max}, $C_{t,}$ and $AUC_{0-t,}$ as applicable) will be applied for pharmacokinetic analysis.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at pre-dose and one-half of the lower limit of quantitation (LLOQ) for post dose time points.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized and descriptive statistics will be provided.

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

Baseline data will include a summary of body weight, height, and body mass index.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

Data from the placebo recipients in all cohorts will be combined to form one placebo group for the purpose of analysis. Each of the GS-6207 and TAF treatment group will be compared to the pooled placebo group with respect to the primary efficacy endpoint, the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10, using the 2-sided t-test conducted at an alpha level of 0.05.

8.5.2. Secondary Analyses

Correlation between C_t of GS-6207 and the maximum reduction of HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 will be assessed using the Pearson correlation analysis. Analysis will be done for each treatment group.

The percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 (for Part A only) will be summarized by treatment group. Fisher exact test will be used for comparison between treatment groups.

Percentage of subjects with any emergence of CAI resistance and TAF resistance, respectively, will be summarized by treatment group.

8.6. Safety Analysis

All safety data collected on or after the first dose date will be summarized by treatment according to the study drug received. Data for the pretreatment period will be included in data listings.

8.6.1. Duration of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration eCRF form. Exposure data 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 that begins on or after the date of first dose of study drug.

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

8.6.3. Laboratory Evaluations

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

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

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline, will be summarized by treatment group. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The post baseline maximum toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital sign and safety ECG data will be summarized and/or listed as appropriate.

8.7. Pharmacokinetic Analysis

The plasma concentration data of GS-6207 and TAF, and its metabolites, will be summarized by nominal sampling time and treatment using descriptive statistics. Pharmacokinetic and PBMC parameters will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum) by treatment group. The concentrations of the study drug in plasma over time will be plotted in semi-logarithmic and linear formats as mean ± standard deviation and median (Q1, Q3), respectively.

8.8. Sample Size

Part A: A sample size of 6 subjects in each GS-6207 treatment group and a total of 10 placebo subjects from all cohorts combined will provide 99% power to detect a treatment difference of 2.79 $\log_{10}$ copies/mL in maximum reduction of HIV-1 RNA between at least one of the GS-6207 treatment groups and the placebo group. In this power analysis, it is assumed that a common standard deviation for maximum reduction in HIV-1 RNA is 0.526 $\log_{10}$ copies/mL (based on Study GS-US-141-1219) and a 2-sided t-test is conducted at an alpha level of 0.05.

Part B: A sample size of 8 subjects in each TAF dose group and a total of 10 subjects in the placebo group will provide 99% power to detect a treatment difference of 1.43 $\log_{10}$ copies/mL in maximum reduction of HIV-1 RNA between at least one of the TAF dose groups and the placebo group from Part A. In this power analysis, it is assumed that a common standard deviation for maximum reduction in HIV-1 RNA is 0.52 $\log_{10}$ copies/mL (based on Studies GS-US-120-0104 and GS-US-120-1101) and a 2-sided t-test is conducted at an alpha level of 0.05.

8.9. Analysis Schedule

Interim Unblinded Analyses

Prior to the final analysis, a few selected individuals from Gilead will be unblinded to assess the interim safety, efficacy, and PK of study drug. This group will consist of at least one representative from Clinical Research, Biostatistics, Clinical Pharmacology, and Pharmacovigilance/Epidemiology, and may include other personnel as necessary. Details of unblinding (eg, memberships, responsibilities, analysis schedules) will be defined in a charter.

1) To select the doses for Cohorts 2 through 5 in Part A

After at least 50% of the subjects and/or after all subjects within each cohort complete the Day 10 visit, the Sponsor will conduct interim unblinded analyses to select the GS-6207 doses to evaluate in each subsequent cohort. The Sponsor will review cumulative safety (through at least Day 14), available viral kinetic, and available PK data. The results from these analyses may be submitted to regulatory agencies to facilitate the clinical development program or to scientific meetings or journals to disseminate the findings.

2) To select the doses for Cohorts 7 and 8 in Part B

After at least 50% of the subjects in each cohort and/or after all subjects within each cohort complete the Day 10 visit, the Sponsor will conduct interim analyses to select the TAF doses to evaluate in each subsequent cohort. The Sponsor will review cumulative safety (through at least Day 14), available viral kinetic, and available PK data. The results from these analyses may be submitted to regulatory agencies to facilitate the clinical development program or to scientific meetings or journals to disseminate the findings.

3) To select the dose(s) for further clinical development

After the last subject in the study completes Day 10 visit, the Sponsor may conduct an interim unblinded analysis of cumulative safety, viral kinetic, and PK data to select the dose(s) for further clinical development (e.g. Phase 2 or 3 studies).

Final analysis

The Sponsor will conduct a final analysis of all data after the last subject in the study completes the last visit (Day 225) or prematurely discontinues from the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

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

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

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

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields

will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. GS-6207 and TAF (Investigational Medicinal Product or Study Drug) and B/F/TAF Accountability and Return

Where possible, IMP and B/F/TAF 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 and B/F/TAF 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 and/or B/F/TAF are destroyed on site, the investigator must maintain accurate records for all IMP and/or B/F/TAF 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 and B/F/TAF supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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VIREAD, Gilead Sciences Inc. VIREAD® (tenofovir disoproxil fumarate) Tablets, for Oral Use. VIREAD® (tenofovir disoproxil fumarate) Powder, for Oral Use. U. S. Prescribing Information. Foster City, CA. Revised: April. 2019:

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1b Randomized, Double-Blinded, Placebo Controlled, Multi-Cohort Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-6207 administered subcutaneously in HIV-1 Infected Subjects

GS-US-200-4072, Amendment 4, 13 June 2019

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

PPD

Name (Printed)
Author

PPD

14 June 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. Study Procedures Table

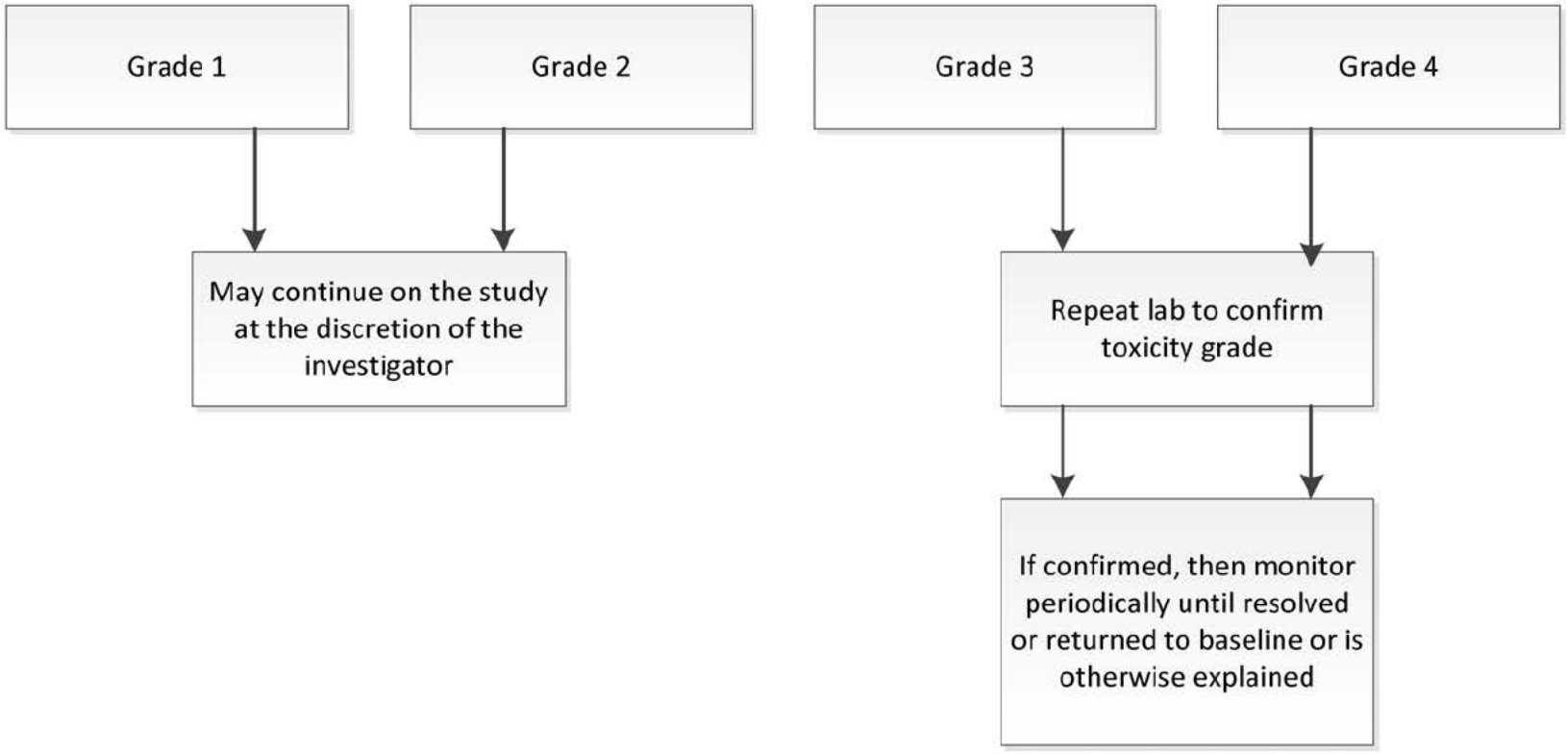
	Screening[a]	Day 1[b, h]	Day 2	Day 3[h]	Day 4	CCI	Day 7[h]	Day 8	Day 9	Day 10[h]	Day 14	Day 29	Day 43	Day 57	Day 85[h]	Day 113	Day 141	Day 169[h]	Day 197	Day 225[h]	Early Termination[d]
Written Informed Consent	X																				
Medical History	X																				
Complete Physical Examination	X	X																			X
Symptom Directed Physical Examination			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[j] (including weight)	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X							X		X		X	X			X		X	
Height	X																				
Hematology[f]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[g]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Estimated GFR[c]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and Urine Chemistry[k]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Urine Storage Sample		X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X											X		X	X	X	X	X	X	X	X
Serum FSH[i]	X																				
Urine Pregnancy test		X																			
HBV, HCV Testing	X																				
CD4+ Cell Count	X	X								X		X	X	X	X	X	X	X	X	X	X
HIV-1 Genotyping/Phenotyping	X																				
HIV-1 capsid Genotype/Phenotype[r]	X									X											

	Screening[a]	Day 1[b,h]	Day 2	Day 3[h]	Day 4	CCI	Day 7[h]	Day 8	Day 9	Day 10[h]	Day 14	Day 29	Day 43	Day 57	Day 85[h]	Day 113	Day 141	Day 169[h]	Day 197	Day 225[h]	Early Termination[d]
HIV DNA genotyping															X			X		X	
Plasma HIV-1 RNA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intensive PK Plasma Collection (Part A)		X[l]																			
Single Anytime PK Plasma Sample (Part A)[n]				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Plasma Sample (Part B)[o]		X	X	X	X		X	X	X	X											
PBMC PK Samples (Part B)[p]		X	X	X	X		X	X	X	X											
CCI																					
GS-6207 Administration (Part A)		X																			
TAF Administration (Part B)		X																			
B/F/TAF dispensation										X			X		X		X		X		
Adverse Events/ Concomitant Meds	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening evaluations must be completed within 42 days prior to Day 1.
b Day 1 tests and procedures must be completed prior to administration of the dose of study drug
c According to the Cockcroft-Gault formula
d Within 72 hours of permanently discontinuing study. Counsel subject regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility.
e Females of childbearing potential only
f Hematology: CBC with differential and platelet count
g Chemistries: Alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing if total amylase > 1.5 × ULN).
h Fasting overnight (≥ 6 hours) required for Days 1, 3, 7, 10, 85, 169 and 225

i FSH test is required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
j Vital signs – blood pressure, pulse, respiration rate, and temperature, weight
k Urinalysis and Urine Chemistry: including color & clarity, specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase and microscopic (if microscopic elements are seen), urine protein, albumin, creatinine, phosphate, calcium, magnesium and uric acid
l Part A: Serial blood samples to determine pharmacokinetics (PK) in plasma will be collected at the following time points relative to study drug dosing 0 (pre-dose), 1, 2,4, 8, 12 and 24 hours post dose.
[redacted]
n Part A: Single Anytime PK sample to be collected at the Day 3, 4, and 7 through 225 visits.
o Part B: Plasma PK samples to be collected at the following time points relative to study drug dosing: 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours post dose; as well as at Days 4, CCI 7, 8, 9 and 10 at approximately the same time in the morning as pre-dose on Day 1.
p Part B: PBMC PK samples to be collected at the following time points relative to study drug dosing: 0 (pre-dose), 1, 2, 4, 6, 8, 12, 24 and 48 hours post dose, as well as at Days 4, CCI , 7, 8, 9 and 10 at approximately the same time in the morning as pre-dose on Day 1.
[redacted]
r Part A: subjects require the HIV-1 capsid genotype/phenotype to confirm eligibility prior to randomization. Part B: the capsid genotype/phenotype will be completed for informational purposes, but it is not be required to confirm eligibility.

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (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
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

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

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

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

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

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

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

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

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

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

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

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

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Schneider 2008}

Appendix 6. GS-6207 Pregnancy Precautions (Part A), Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 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.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-6207 is contraindicated in pregnancy as a malformation effect has been demonstrated/suspected or is unknown, taking into consideration class effects, genotoxic potential, or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. GS-6207 has demonstrated/suspected or has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Day 1 prior to first dose of study drug. Pregnancy tests will be performed as defined by the schedule of assessments in Appendix 2. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. Female subjects of childbearing potential must agree to one of the following from Screening until 300 days following the administration 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

  — 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)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 300 days after the administration of study drug.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners must use condoms during treatment and until 360 days after the administration of study drug. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 360 days after the administration of study drug.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect that they are pregnant at any time during the study or if they become pregnant within 300 days after the administration of study drug. A male subject whose partner has become pregnant or suspects she is pregnant during the study or within 360 days of the male subject's administration of study drug must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 7. TAF Pregnancy Precautions (Part B), Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 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.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of TAF have demonstrated no adverse effect on fertility or embryo-fetal development. However, the data on TAF in pregnant women is limited or not available. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 prior to first dose of study drug. Pregnancy tests will be performed as defined by the schedule of assessments in Appendix 2. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until 7 days after the last dose of Biktarvy during the study. If Biktarvy is not initiated, one of the following contraception requirements should be followed until 10 days after the dose of TAF.

- 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 (Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study drug dosing.)
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 7 days after the last dose of Biktarvy on the study. If Biktarvy is not initiated, female subjects must also refrain from egg donation and in vitro fertilization after TAF administration and until at least 10 days after the dose of TAF.

3) Contraception Requirements for Male Subjects

During treatment on the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential, and male subjects must also refrain from sperm donation.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 7 days of the last dose of Biktarvy on the study. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discuss with the investigator whether to continue Biktarvy. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.7.2.1.