CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination with Other Antiretroviral Agents in People Living with HIV
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	136260
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT04143594
Indication:	HIV-1 Infection
Protocol ID:	GS-US-200-4334
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 02 October 2019 Amendment 1: 05 November 2019 Amendment 2: 24 January 2020 Amendment 3: 01 September 2020 Amendment 4: 04 February 2022

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

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination with Other Antiretroviral Agents in People Living with HIV
IND Number: **EudraCT Number:** **ClinicalTrials.gov Identifier:**	136260 Not Applicable NCT04143594
Study Centers Planned:	Approximately 75 centers in North America and Latin America
Objectives:	The primary objective of this study is: • To evaluate the efficacy of GS-6207 (Lenacapavir, LEN) containing regimens in people living with HIV (PLWH) as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 The secondary objectives of this study are: • To evaluate the efficacy of GS-6207 containing regimens in PLWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 • To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80 • To evaluate the safety and tolerability of the GS-6207 containing regimens through 28, 38, 54, and 80 weeks of treatment • To evaluate the pharmacokinetics (PK) of GS-6207, BIC, and TAF CCI [redacted]

CCI [redacted]

Study Design:	This is a Phase 2, randomized, open label, active controlled, multicenter study. Treatment-naive PLWH who meet all eligibility criteria will be randomized in a 2:2:2:1 ratio to 1 of the 4 treatment groups. Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at Screening. **Treatment Group 1 (n = 50)** Induction: GS-6207 600 mg oral on Day 1 and Day 2, GS-6207 300 mg oral on Day 8, then subcutaneous (SC) GS-6207 927 mg on Day 15 + oral daily emtricitabine/tenofovir alafenamide (F/TAF) (200/25 mg) from Day 1 onwards for a total of 28 weeks Maintenance: SC GS-6207 927 mg on Week 28 and every 26 weeks + oral daily TAF (25 mg) **Treatment Group 2 (n = 50)** Induction: GS-6207 600 mg oral on Day 1 and Day 2, GS-6207 300 mg oral on Day 8, then SC GS-6207 927 mg on Day 15 + oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks Maintenance: SC GS-6207 927 mg on Week 28 and every 26 weeks + oral daily bictegravir (BIC) (75 mg) from Week 28 onwards **Treatment Group 3 (n = 50)** GS-6207 600 mg oral on Day 1 and Day 2 then oral daily GS-6207 50 mg + oral daily F/TAF (200/25 mg) from Day 1 onwards **Treatment Group 4 (n = 25)** Oral daily B/F/TAF (50/200/25 mg)
Number of Participants Planned:	Approximately 175 participants will be enrolled in this study. 50 participants may be enrolled in Treatment Group 1 50 participants may be enrolled in Treatment Group 2 50 participants may be enrolled in Treatment Group 3 25 participants may be enrolled in Treatment Group 4
Target Population:	Treatment naïve PLWH ≥ 18 years of age.

Duration of Treatment:	Duration of treatment is at least 80 weeks. Participants in Treatment Group 4 will complete the study at Week 80. Following successful completion of Week 80 visit, participants receiving GS-6207 will be given the option to receive further treatment and continue to attend visits on Week 90, Week 106, Week 116, Week 132, Week 142, and will continue to alternate between every 10 weeks and every 16 weeks visits. Participants willing to continue the study beyond Week 80 in Treatment Groups 1 and 2 will continue to receive SC GS-6207 927 mg every 6 months (26 weeks) from Week 80 onwards and participants in Treatment Group 3 will receive oral GS-6207 50 mg daily from Week 80 until the product becomes accessible to participants through an access program, or until Gilead elects to discontinue the study in the country. Participants in Treatment Groups 1, 2, and 3 will also receive TAF, F/TAF, or BIC as applicable. Participants who discontinue study drugs prior to Week 80 visit or prior to study completion may be required to complete 30-Day, 90-Day and/or 180-Day Follow Up visits after Early Termination Visit.
Diagnosis and Main Eligibility Criteria:	Treatment naive PLWH who meet the following criteria: • Age ≥ 18 years of age at Screening • Plasma HIV-1 RNA ≥ 200 copies/mL at Screening • CD4+ cell count ≥ 200 cells/μL at Screening • Antiretroviral naive with no use of any ARV within one month of Screening. Use of pre-exposure prophylaxis (PrEP) (any duration), post-exposure prophylaxis (PEP) (any duration), or HIV-1 treatment (< 10 days therapy total) > 1 month prior to Screening is permitted.
Study Procedures/ Frequency:	At Screening, laboratory analyses (hematology, chemistry and urinalysis and serum pregnancy test [for women]), HIV-1 RNA, CD4+ cell count, vital signs, electrocardiogram (ECG), complete physical examination and estimated glomerular filtration rate (eGFR) will be performed, and hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies will be analyzed.CCI [redacted] After screening procedures, eligible participants will be randomized into one of the four treatment groups in a 2:2:2:1 ratio. Participants in Treatment Groups 1, 2, and 3 only, will have visits on Day 1, Day 2, CCI [redacted] Day 8, and Day 15. All

participants will have a Week 4 visit and will continue to attend study visits every 6 weeks until Week 28.

Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study drug at or prior to Week 28.

After Week 28, participants will attend study visits on Week 38, Week 54, Week 64, and Week 80. After Week 80, participants in Treatment Group 4 will complete the study and participants in Treatment Groups 1, 2, and 3 will be given the option to receive further treatment and continue to attend visits alternating between every 10 weeks and every 16 weeks visits.

At each visit, adverse events (AEs), concomitant medications, laboratory tests and physical examinations will be performed in accordance with the Study Procedures Table (Appendix 2).

Pharmacokinetic Assessments:

For Treatment Groups 1 and 2:

Plasma PK sampling will occur relative to dosing of GS-6207 at the following time points for all participants:

- Days 1, 2, and 8:
  - — Predose (within 30 minutes of dosing)
  - — A single timed PK sample between 1 and 6 hours postdose
- [redacted]
- At Day 15 and at all visits with SC GS-6207 injections: A single predose PK sample will be collected
- Starting at Week 4 visit, at all visits without SC GS-6207 injections: A single anytime PK sample will be collected

CCI [redacted]

CCI [redacted]

CCI [redacted]

For Treatment Group 3:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits

CCI [redacted]

For Treatment Group 4:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits.

Patient Reported Outcomes (PROs) (if available):

- HIV Dependent Quality of Life (HIVDQoL) and EQ-ED-5L at Day 1, Weeks 4, 28, 54 and 80
- HIV Treatment Satisfaction Questionnaire (HIVTSQ12) at Day 15, Weeks 4, 28, 54 and 80
- The Injection Acceptability Scale and Numeric Pain Rating Scale at Day 15, Weeks 28, 54 and 80 (for Treatment Groups 1 and 2 participants only)

Test Product, Dose, and Mode of Administration:

Treatment Group 1

Induction: Oral GS-6207, SC GS-6207, and oral F/TAF

Maintenance: SC GS-6207 and oral TAF

Treatment Group 2

Induction: Oral GS-6207, SC GS-6207, and oral F/TAF

Maintenance: SC GS-6207 and oral BIC

Treatment Group 3

Oral GS-6207 and oral F/TAF

Participants in Group 1 and Group 2 may require oral weekly bridging 300 mg if a SC injection of GS-6207 cannot be administered for any reason within the protocol visit window.

Reference Therapy, Dose, and Mode of Administration:

Treatment Group 4

Oral B/F/TAF

None after Week 80

Criteria for Evaluation:

Safety: Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities

Efficacy: The primary endpoint of this study is:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the Food and Drug Administration (FDA)-defined snapshot algorithm

The secondary endpoints of this study are:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the FDA-defined snapshot algorithm
- The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80

Pharmacokinetics: The following PK parameters will be calculated for GS-6207, TAF, and BIC (and metabolites, as appropriate) in plasma, as appropriate.

CCI [redacted]

$AUC_{0\text{-}t}$, AUC_{tau}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, C_t

Statistical Methods: The primary efficacy analysis is to compare the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US FDA-defined snapshot algorithm. Point estimates and 95% confidence interval (CI) for the difference in the response rates between each of the GS-6207-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) will be constructed using normal approximation method, stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL). The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 respectively, as determined by the US FDA-defined snapshot algorithm will be analyzed using the same methods as for the primary efficacy endpoint. Baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) adjusted differences in change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Weeks 28, 38, 54, and 80 between each of the GS-6207-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Groups 4) and the associated

95% CIs will be constructed using analysis of variance (ANOVA) models.

Incidence of TEAEs and treatment-emergent laboratory abnormalities will be summarized using descriptive statistics.

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

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BIC	Bictegravir, B
BCRP	breast cancer resistance protein
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BMI	body mass index
BLQ	below the limit of quantitation
bpm	beats per minute
BUN	blood urea nitrogen
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CAI	capsid inhibitor
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CMH	Cochran-Mantel-Haenszel
COBI	cobicistat
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization
CSR	clinical study report

C_t	observed drug concentration
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-Drug Interaction
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DRV	darunavir
EC	ethics committee
ECG	Electrocardiogram
EFV	Efavirenz
eCRF	electronic case report form
EDC	electronic data capture
eGFR	Estimated glomerular filtration rate
EudraCT	European Clinical Trials Database
eSAE	electronic serious adverse event
ET	early termination
eTMF	Electronic trial master file
EU	European Union
FAM	famotidine
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
F/TAF	emtricitabine/tenofovir alafenamide
FTC	Emtricitabine
GD	Gestation Day
GGT	gamma-glutamyltransferase
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus, type 1
HIVDQoL	HIV Dependent Quality of Life
HIVTSQ12	HIV Treatment Satisfaction Questionnaire
HLGT	high-level group term
HLT	high-level term

IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	Independent ethics committee
IND	investigational new drug (application)
INSTI	Integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	institutional review board
IV	intravenous
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantitation
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
NaS	Sodium Salt
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitors
PIT	pitavastatin
PBMC	Peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PEP	Post-exposure prophylaxis
PI	protease inhibitor
PopPK	population pharmacokinetic
PrEP	Pre-exposure prophylaxis
PRO	Patient Reported Outcomes
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLWH	people living with HIV
PPI	proton pump inhibitors
PT	Preferred Term
GLPS	Global Patient Safety (formerly Pharmacovigilance and Epidemiology)
QD	once daily
RIP	rifampin
ROS	rosuvastatin
RAL	raltegravir
SAC	Safety Assessment Committee

SADR	serious adverse drug reaction
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SSR	special situation report
SVR	suboptimal virologic response
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of Clast
T_{max}	the time (observed time point) of C_{max}
TFV	Tenofovir
TFV-DP	tenofovir diphosphate
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of normal
US, USA	United States, United States of America
VORI	Voriconazole
VR	virologic rebound
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 living with HIV (PLWH) worldwide including approximately 16 million on antiretroviral (ARV) treatment {UNAIDS 2018}. 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 nucleoside reverse transcriptase inhibitors [NRTIs] plus a third agent) to suppress viral replication to below detectable limits, increase CD4 cell counts, and delay disease progression.

While combination ART 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, which is defined as "decreased desire and motivation to maintain vigilance in adhering to a treatment regimen" among PLWH 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 PLWH. In addition, some PLWH may benefit from combination HIV therapy using GS-6207.

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. GS-6207 has been assigned the International Nonproprietary Name Lenacapavir (LEN).

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 pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2. Clinical Studies of GS-6207

A summary of the relevant available data from studies not yet included in the IB is presented. These data are from four Phase 1 clinical studies in healthy volunteers (GS-US-200-4071, GS-US-200-4333, and GS-US-200-4538) and one study in PLWH (GS-US-200-4072). Participants in study GS-US-200-4072 received injections of a subcutaneous (SC) GS-6207 suspension formulation that will not be used in this protocol. Studies GS-US-200-4071 and GS-US-200-4538 used the tablet and SC solution formulations, respectively, that will be used in this study.

1.2.2.1. GS-US-200-4071

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 oral GS-6207 as an oral liquid (solution)-filled capsule (50 mg/mL or 100 mg/mL) or tablet (50 mg or 300 mg). As of 03 September 2019, a total of 50 unique participants have received GS-6207 or placebo capsules and 46 unique participants have received GS-6207 or placebo tablets. Single and multiple dose PK data from the 50 mg/mL solution filled capsule, and single dose PK data from the tablets are presented below. To reduce pill burden, the GS-6207 tablet will be the oral form used in this study.

This study was originally designed as a SAD/MAD evaluation of solution in capsule formulations, with 10 days of washout between the single dose and multiple dose periods (Cohorts 1 and 2). Following receipt of PK data from these 2 cohorts suggesting the $t_{1/2}$ was longer than predicted, the study design was altered to be single ascending dose.

Within each cohort, participants were randomized to receive GS-6207 (N = 8) or placebo (N = 2); all treatments were administered under fasted conditions, unless otherwise specified. In Cohorts 1, 2 and 5, capsules containing 50 mg/mL solution were evaluated at doses of 30, 100, and 300 mg, respectively. Following development of a tablet formulation, 50 mg and 300 mg tablets were assessed in which participants were randomized to receive GS-6207 (N = 8) or placebo (N = 2) under fasted conditions. In addition, two cohorts received open-label 300 mg GS-6207 tablets (N = 8) given with a high fat, high calorie meal or with a low fat, low calorie meal. A brief description of all cohorts is presented in Table 1-1.

Table 1-1. GS-US-200-4071: GS-6207 Formulations and Doses Evaluated

Formulation Description	Dose (# capsules/fasting status)
Single dose solution in capsule	
50 mg/mL	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted) 300 mg (8 capsules, fasted)
Multiple dose solution in capsule	
50 mg/mL	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted)
Single dose tablet	
50 mg	50 mg (1 tablet, fasted)
300 mg	300 mg (1 tablet, fasted) 900 mg (3 tablets, fasted) 1800 mg (6 tablets, fasted) 300 mg (1 tablet, high fat)[a] 300 mg (1 tablet, low fat)[a]

a high fat meal included high calorie count (~1000 kcal, ~50% fat), low fat meal included low calorie count (~400 kcal, ~25% fat)

Pharmacokinetic Results

GS-6207 concentration-time profiles and preliminary PK parameters after administration of single oral doses of GS-6207 oral solution in capsules are presented in Figure 1-1 and Table 1-2, respectively. Maximum plasma concentrations of GS-6207 (C_{max}) occurred between 7 and 29 hours (median T_{max}), and the median $t_{1/2}$ of GS-6207 was approximately 12 days. Within each increase in dose, the increase in C_{max} was less than dose proportional, suggesting GS-6207 exhibits solubility-limited absorption.

Figure 1-1. **GS-US-200-4071: Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-6207 Solution in Capsule (50 mg/mL; N = 8/cohort)**

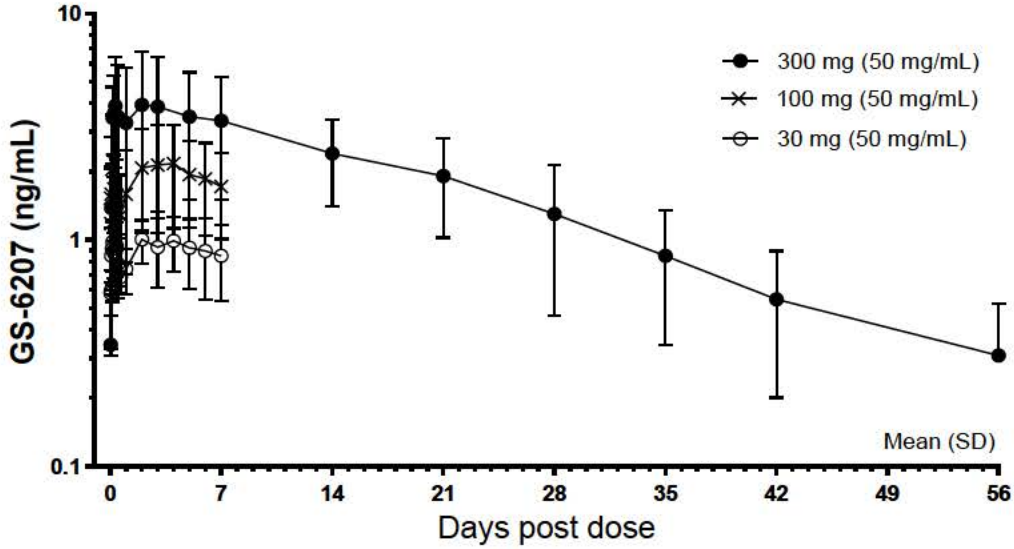


Table 1-2. **GS-US-200-4071: Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Single Dose Oral Administration of 50 mg/mL Solution in Capsule (N = 8 per cohort)**

Parameter	Cohort 1; 30 mg (N = 8)	Cohort 2; 100 mg (N =8)	Cohort 5; 300 mg (N = 8)
C_{max} (ng/mL)	1.16 (23.9)	2.70 (55.4)	4.75 (52.4)
t_{max} (hr)†	29.0 (4.00, 90.0)	26.0 (4.00, 96.0)	7.00 (4.00, 18.00)
AUC_{last} (hr*ng/mL)[a]	147 (29.0)	319 (46.0)	1990 (52.0)
AUC_{inf} (hr*ng/mL)	ND	ND	2280 (53.1)
AUC %Extrapolated (%)	ND	ND	11.6 (61.0)
AUC_{0-24} (hr*ng/mL)	17.6 (19.7)	34.8 (47.3)	75.7 (61.3)
$t_{1/2}$†(days)	ND	ND	12.3 (10.7, 13.8)

PK parameters are presented as Mean (%CV), and shown to 3 significant digits; SD = single dose; ND = not determined due to insufficient PK sampling; †Median (Q1,Q3); [a] AUC_{last} calculated through Day 7 post dose for Cohorts 1 and 2 and through last currently available timepoint for Cohort 5; AUC_{0-24hr} = AUC from time zero through 24 hours post dose

GS-6207 preliminary PK parameters after 10 daily oral doses of GS-6207 (50 mg/mL solution in capsule) are presented in Table 1-3. Consistent with its half-life, following 10 days of multiple dosing, the mean GS-6207 C_{max} and AUC_{0-24} were at least 10-fold higher than those after a single dose (Table 1-2 and Table 1-3).

Table 1-3. GS-US-200-4071: Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Multiple Dose Oral Administration of 30 mg and 100 mg Solution in Capsule (50 mg/mL) (N = 8 per cohort)

Parameter	Cohort 1; 30 mg (N = 8)	Cohort 2; 100 mg (N = 8)
	50 mg/mL solution in capsule	
C_{max} (ng/mL)	12.2 (17.1)	41.3 (53.8)
t_{max} (hr)†	3.50 (1.89, 10.0)	4.00 (4.00, 10.5)
AUC_{0-24hr} (hr*ng/mL)	232 (17.9)	843 (56.5)

%CV = percentage coefficient of variation; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits
†Median (Q1, Q3)

GS-6207 concentration-time profiles and preliminary PK parameters after administration of single doses of GS-6207 oral tablets administered either under fasted conditions, or with a high fat or low fat meal, are presented in Figure 1-2 and Figure 1-3, and Table 1-4. Interim safety and PK data are available through at least 8 days postdose. Based on preliminary PK data, GS-6207 exposures increased in a less than dose-proportional manner over the dose range of 50 mg to 1800 mg. Maximal concentrations (C_{max}) of GS-6207 were achieved approximately 4 to 8 h postdose (T_{max}), and GS-6207 half-life ($t_{1/2}$) is estimated to be approximately 12 days (Table 1-4).

Exposure (C_{max} and AUC_{0-D8}) and time to maximal exposure (T_{max}) were comparable following administration of GS-6207 300 mg tablets under fasted conditions or with a high or low fat meal; thereby, supporting dosing of GS-6207 tablets with or without food in future clinical trials (Table 1-4).

Figure 1-2. **GS-US-200-4071: Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Oral Administration of GS-6207 Tablets, Fasted (N = 8/cohort)**

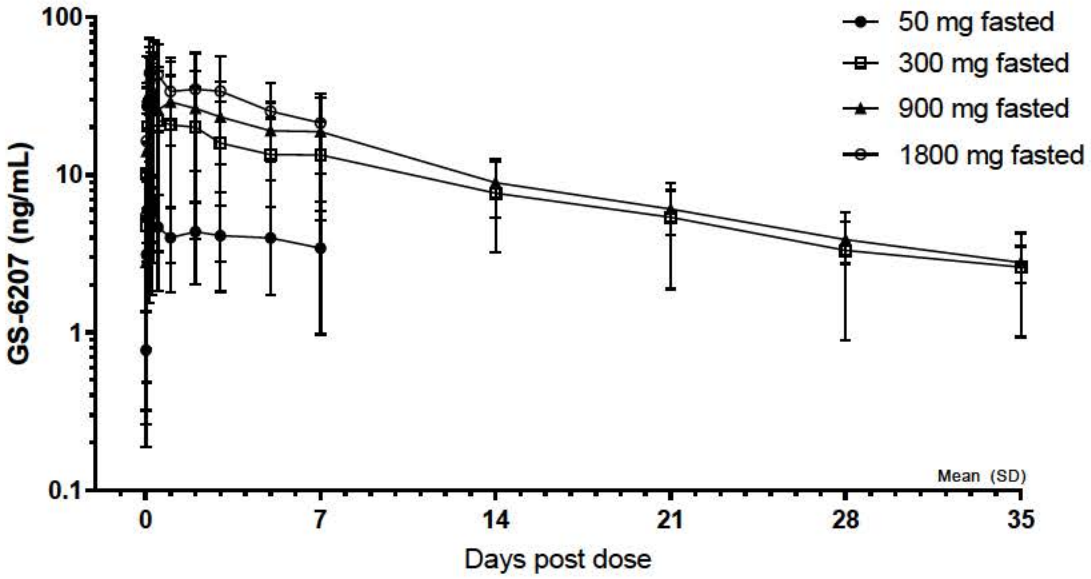


Figure 1-3. **GS-US-200-4071: Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-6207 300 mg Tablets, Administered Fasted or with a High Fat or Low Fat Meal (N = 8/cohort)**

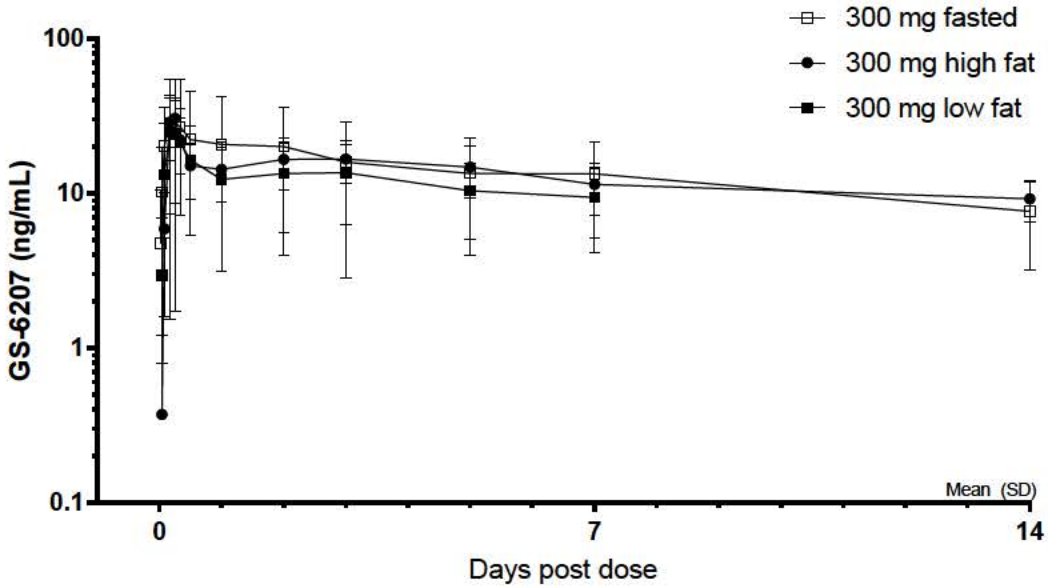


Table 1-4. GS-US-200-4071: Preliminary Plasma Pharmacokinetic Parameters Following Single Dose Oral Administration of GS-6207 Tablets, Fasted, or Following a High or Low Fat Meal (N = 8 per cohort)

Parameter	50 mg (N = 8)	300 mg (N = 8)	900 mg (N = 8)	1800 mg (N = 8)	300 mg + High Fat Meal (N = 8)	300 mg + Low Fat Meal (N = 8)
AUC_{inf} (hr*ng/mL)	NC	7990 (56.1)	9900 (44.9)	NC	NC	NC
$AUC_{0\text{-}D8}$ (hr*ng/mL)[a]	694 (56.0)	2790 (81.5)	3900 (67.2)	5080 (56.3)	2540 (33.6)	2060 (55.7)
C_{max} (ng/mL)	8.24 (48.3)	33.7 (96.3)	43.9 (73.3)	53.8 (48.0)	35.0 (33.0)	28.1 (60.6)
T_{max} (hr)	4.00 (4.00, 5.50)	4.00 (4.00, 6.00)	4.00 (2.50, 20.0)	8.00 (5.00, 8.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)
$T_{1/2}$ (h) [days]	NC	265 (223, 349) [11.0]	322 (237, 333) [13.4]	NC	NC	NC

PK parameters are presented as Mean (%CV) except T_{max} and $T_{1/2}$ which are presented as median (Q1,Q3) and shown to 3 significant digits; NC = not calculated due to insufficient PK sampling;
a $AUC_{0\text{-}D8}$ calculated through Day 8 postdose

Safety Results

Safety data as of 03 September 2019 are available for 56 participants who have received oral GS-6207 tablets or matched placebo in one of 6 dosing cohorts.

GS-6207 tablets were generally safe and well tolerated across all treatment groups. A total of 9 of 56 participants (16.1%) had at least 1 adverse event (AE) reported. The most commonly reported AEs were headache (n = 3, 5.4%) and back pain (n = 2, 3.6%). No other AEs were reported by more than one participant. No Grade 3 or 4 AEs, deaths, serious adverse events (SAEs), pregnancy, or AEs leading to permanent discontinuation of study drug were reported in any treatment group.

In a preliminary blinded review of safety data as of 03 September 2019, when all participants who had received GS-6207 solution in capsules or placebo-to-match had completed or discontinued the study, the safety profile was similar to that observed with the tablets. The only AE reported for > 1 participant was headache (6.7%, 2 participants).

1.2.2.2. GS-US-200-4072

GS-US-200-4072 is an ongoing, Phase 1b, randomized, double-blinded, placebo-controlled, multi-cohort dose-ranging study evaluating the safety, tolerability, PK, and short-term antiviral activity of monotherapy with SC doses of a GS-6207 free acid suspension (100 mg/mL) in PLWH who are either ART naive or ART experienced but capsid inhibitor (CAI) naive.

This study will enroll 5 cohorts of approximately 8 unique participants per cohort to receive GS-6207 or placebo. Within each Cohort (n = 8), participants are 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 is administered as SC injection(s) in the abdomen on Day 1.

As of 25 July 2019, 32 participants have been administered SC GS-6207 or placebo (3:1 ratio) at doses of 20 mg, 50 mg, 150 mg, and 450 mg. Enrollment of a fifth cohort to receive GS-6207 750 mg is ongoing. Interim blinded data for participants who received GS-6207 20 mg to 450 mg are presented below.

Disposition and Baseline Characteristics

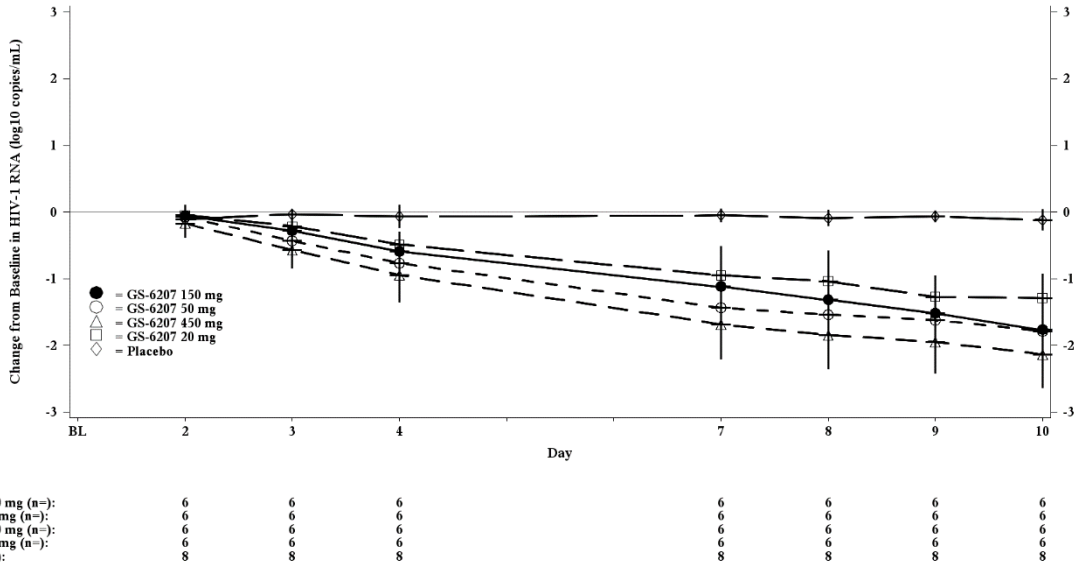
As of 25 July 2019, 32 participants have been randomized and received a single dose of SC GS-6207 or placebo. All participants are continuing in study follow up. The median duration of follow-up (number of days between Day 1 and the last study date) ranged from 38 to 199 days across the 4 cohorts.

The majority of participants were male (93.8%), white (56.3%), and not Hispanic or Latino (90.6%). The median age was 34 years (range: 19−59 years). The median (Q1, Q3) baseline HIV-1 RNA was 4.48 (4.27, 4.68) $\log_{10}$ copies/mL, and the median (Q1, Q3) CD4 cell count was 458 (361, 594) cells/μL. The majority of participants were ART naive (78.1%).

Efficacy Results

As of 25 July 2019, 32 participants have been randomized and received a single dose of SC GS-6207 or placebo. HIV-1 RNA levels decreased following initiation of study drug Figure 1-4). The mean (SD) maximum HIV-1 RNA reductions from baseline through Day 10 were 1.35 (0.318), 1.79 (0.476), 1.76 (0.203), and 2.20 (0.468) $\log_{10}$ copies/mL at doses of GS-6207 20 mg, 50 mg, 150 mg, and 450 mg, respectively. All participants who received ≥ 50 mg GS-6207 had a > 1 $\log_{10}$ copies/mL reduction in their HIV-1 RNA through Day 10. Overall, antiviral activity was comparable across the dose range of 50 mg to 450 mg but lower at the 20 mg dose.

Figure 1-4. GS-US-200-4072: Mean and 95% CIs Change from Baseline in HIV-1 RNA (log_{10} copies/mL) (Full Analysis Set)



GS-6207 150 mg (n=):	6	6	6	6	6	6	6
GS-6207 50 mg (n=):	6	6	6	6	6	6	6
GS-6207 450 mg (n=):	6	6	6	6	6	6	6
GS-6207 20 mg (n=):	6	6	6	6	6	6	6
Placebo (n=):	8	8	8	8	8	8	8

Pharmacokinetic Results

Preliminary PK data show that following 50, 150, and 450 mg doses of GS-6207 SC suspension mean GS-6207 concentrations on Day 10 are 1.1- to 9.9-fold higher than the protein adjusted (pa)EC_{95} for wild type HIV-1 based on the EC_{50} in MT-4 cells (inhibitory quotient [IQ] = 1.1, 3.3, and 9.9, for the 50, 150, and 450 mg doses, respectively).

Safety Results

As of 25 July 2019, no deaths, Grade 4 AEs, or AEs leading to study drug discontinuation have been reported to date. One participant experienced a Grade 3 SAE of atrial fibrillation which occurred following methamphetamine use and was not considered related to study drug by the investigator. No other serious or Grade 3 AEs were reported. Most (24 of 32, 75%) participants reported an AE. The most frequent AEs were injection site pain (40.6%), injection site erythema (28.1%), and injection site induration (21.9%).

Six participants (18.8%) had a Grade 3 or Grade 4 laboratory abnormality reported.
One participant had a Grade 4 laboratory abnormality reported; a Grade 4 creatine kinase elevation with a concurrent Grade 3 aspartate aminotransferase (AST) elevation both attributed to exercise. The Grade 3 or 4 abnormalities reported for more than one participant were: transient creatine kinase elevations, both attributed to recent exercise, (n = 2).

No notable changes from predose in vital signs (systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiration rate) have been observed in the study. No clinically significant ECG abnormalities have been reported.

1.2.2.3. GS-US-200-4329

GS-US-200-4329 is an ongoing Phase 1 study in healthy volunteers evaluating the safety, tolerability, PK, metabolism, and excretion of a single intravenous dose (IV) of GS-6207. As of 17 November 2019, a total of 21 unique participants have received GS-6207 or placebo as a 1-hour IV infusion. In Cohort 1, 11 participants received 10 mg GS-6207 or placebo (unlabeled; N = 8 GS-6207 and N = 3 placebo), and in Cohort 2, 10 participants received 20 mg GS-6207 containing a mixture of unlabeled GS-6207 and a [^{14}C]-GS-6207 (equivalent to ~200 uCi). Safety, PK, and radioactivity analysis is ongoing.

Preliminary radioactivity data through Day 78 postdose in Cohort 2 indicate < 1% of the total dose is recovered in the urine and > 80% of the total dose is recovered in the feces, suggesting renal elimination is a minor pathway for GS-6207.

1.2.2.4. GS-US-200-4333

GS-US-200-4333 is an ongoing, Phase 1, open-label, parallel-design, single- and multiple-dose, multiple-cohort study in healthy volunteers evaluating the drug-drug interaction (DDI) potential of GS-6207. Available preliminary data of administration of GS-6207 capsules administered in combination with known strong cytochrome P450 enzyme (CYP)3A/P-glycoprotein (P-gp) inhibitors, darunavir (DRV)/cobicistat (COBI) and COBI, or GS-6207 tablets in combination with a strong CYP3A/UGT/P-gp inducer, rifampin (RIF), an acid reducing agent, famotidine (FAM), and organic anion transporting polypeptide (OATP), breast cancer resistance protein (BCRP), P-gp or CYP3A substrates, pitavastatin, rosuvastatin (ROS), TAF and midazolam (MDZ), respectively are presented below. Evaluation of GS-6207 PK following co-administration with voriconazole (VORI), atazanavir/COBI (ATV/co), or efavirenz (EFV) has not yet been completed.

Cohort 1 served as a reference arm for Cohorts 2 and 3; participants received a single dose of GS-6207 300 mg alone (N = 30). Participants in Cohorts 2 and 3 received up to 90 days of COBI 150 mg QD, or DRV/COBI 800/150 mg QD, respectively, with a single dose of GS-6207 300 mg coadministered in the morning on Day 11 (N = 29 per cohort). All doses were administered in the morning under fed conditions. Pharmacokinetic samples were obtained up to Day 63 (Cohort 1) and up to Day 35 (Cohorts 2 and 3) to characterize the PK of GS-6207 in each treatment. Safety data analysis is ongoing.

Preliminary PK data are presented below (Table 1-5). Median maximum plasma concentrations of GS-6207 (C_{max}) occurred between 6 to 8 hours (T_{max}), and the median $t_{1/2}$ of GS-6207 administered alone was 12.3 days, and ranged from 16.8 to 18.8 days following administration with DRV/co or COBI. Coadministration of DRV/COBI or COBI with GS-6207 resulted in an approximate 2-fold increase in C_{max} and AUC_{inf}. This 2-fold increase in GS-6207 exposure was not deemed clinically relevant, based on safety data from ongoing Phase 1 studies at or above exposures anticipated to be achieved following administration of GS-6207 with strong CYP3A/P-gp inhibitors. Accordingly, the use of strong CYP3A and P-gp inhibitors is permitted with GS-6207.

Table 1-5. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of GS-6207 300 mg Oral Capsule Following Administration Alone or with DRV/COBI (800/150 mg QD) or COBI (150 mg QD) [N = 29-30 per cohort]

Parameter	GS-6207 Alone 300 mg (N = 30)	GS-6207 300 mg + COBI (N = 29)	GS-6207 300 mg + DRV/COBI (N = 29)
C_{max} (ng/mL)	30.6 (74.4)	57.8 (53.6)	61.5 (43.4)
AUC_{last} (h*ng/mL)	10,400 (77.7)	16,100 (61.3)	14,200 (47.3)
AUC_{inf} (h*ng/mL)	10,700 (76.8)	22,700 (62.5)	19,500 (48.7)
T_{max} (hours)	8.00 (6.00, 48.0)	8.00 (6.00, 48.0)	6.00 (6.00, 8.00)
$t_{1/2}$ (days)	12.3 (9.97, 15.9)	18.8 (15.9, 24.2)	16.8 (14.5, 19.3)

%CV = percentage coefficient of variation; COBI = cobicistat; DRV = darunavir; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as Mean (%CV) except T_{max}, $t_{1/2,}$ and $T_{last,}$ which are presented as median (Q1, Q3), and shown to 3 significant digits

Cohort 4 served as a reference arm for Cohorts 8 and 10; in Cohort 4, participants received a single dose of GS-6207 300 mg tablet alone (N = 27). Participants in Cohort 8 received 25 days of RIF (600 mg QD), with GS-6207 administered on Day 14, and participants in Cohort 10 received a single dose of FAM (40 mg) 2 hours prior to a GS-6207 on Day 1 (N = 25 per cohort). All GS-6207 doses were administered in the morning under fasted conditions. Pharmacokinetic samples were obtained up to Day 23 post GS-6207 dose (Cohorts 4 and 10) and up to Day 12 post dose (Cohort 8) to characterize the PK of GS-6207 in each treatment. Safety data analysis is ongoing.

The median $t_{1/2}$ of GS-6207 administered alone was 13.4 days (Table 1-6). Following co-administration with RIF, GS-6207 C_{max} and AUC_{inf} were approximately 2.5-fold and 5-fold lower, respectively, with a corresponding ~5-fold decrease in $t_{1/2}$. These data support the existing recommendations to disallow use of strong inducers with GS-6207.

Following co-administration with FAM, no change in GS-6207 exposure or $t_{1/2}$ was observed; accordingly, use of famotidine and other acid reducing agents is permitted with GS-6207.

Table 1-6. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of GS-6207 300 mg Tablet Following Administration Alone or with RIF (600 mg QD) or FAM (40 mg) [N = 25-27 per cohort]

Parameter	GS-6207 Alone 300 mg (N = 27)	GS-6207 300 mg +RIF (N = 25)	GS-6207 300 mg +FAM (N = 25)
C_{max} (ng/mL)	20.4 (102)	8.17 (59.6)	18.6 (60.2)
AUC_{last} (h*ng/mL)	3880 (65.3)[a]	745 (48.1)[b]	4610 (58.3)
AUC_{inf} (h*ng/mL)	5430 (58.0)[a]	786 (47.7)[b]	6360 (52.9)
$\%AUC_{exp}$	30.0 (24.6)[a]	5.20 (50.7)	28.5 (24.7)
T_{max} (hours)	4.00 (4.00, 6.00)	24.0 (24.0, 48.0)	10.0 (4.00, 48.0)
$t_{1/2}$ (hours)[days]	321 (261, 374) [13.4][a]	63.8 (59.5, 71.1) [2.66][b]	270 (250, 331) [11.3]
T_{last} (days)	23.0 (23.0, 23.0)	12.0 (12.0, 12.0)	23.0 (23.0, 23.0)

[a] N= 25; [b] = N=24; %CV = percentage coefficient of variation; FAM = famotidine; RIF = rifampin; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2}$, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

In Cohort 11, participants received PIT, ROS, TAF and MDZ alone, or co-administered with oral GS-6207. Agents were either co-dosed with oral GS-6207 to evaluate the worst-case (co-administration; PIT, ROS, TAF and MDZ), or up to 3 days after the last dose of GS-6207 (PIT, MDZ) to evaluate the systemic drug interaction liability of GS-6207. Mean concentrations of GS-6207 were at, or above clinically relevant C_{max} concentrations (> 100 ng/mL) throughout the drug interaction evaluation (data not shown). Preliminary PK data are presented in Table 1-7, Table 1-8, Table 1-9 and Table 1-10; Safety data analysis is ongoing.

Table 1-7. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of PIT (2 mg) Following Administration Alone or with GS-6207 (N = 30-31)

Parameter	PIT Alone (N = 31)	PIT+ GS-6207 (Day 15; Co-administration) (N = 30)	PIT + GS-6207 (Day 27; 3 Days Post GS-6207 Dose) (N = 30)
C_{max} (ng/mL)	31.4 (52.8)	31.0 (48.1)	26.8 (50.5)
AUC_{last} (h*ng/mL)	85.7 (44.9)[a]	96.8 (47.8)	76.2 (37.7)[b]
AUC_{inf} (h*ng/mL)	90.9 (43.7)[a]	102 (46.9)	81.5 (36.1)[b]
T_{max} (hours)	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
$t_{1/2}$ (hours)	11.7 (8.56, 13.5)[a]	10.9 (7.41, 14.7)	14.1 (10.2, 16.5)[b]
T_{last} (hours)	36.0 (24.0, 48.0)	36.0 (24.0, 48.0)	36.0 (24.0, 48.0)

[a] N=30; [b] N=26; %CV = percentage coefficient of variation; PIT = pitavastatin; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2}$, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 1-8. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of ROS (5 mg) Following Administration Alone or with GS-6207 (N = 30)

Parameter	ROS Alone (N = 33)	ROS+ GS-6207 (Day 18; Co-administration) (N = 28)
C_{max} (ng/mL)	1.06 (39.5)	1.87 (65.8)
AUC_{last} (h*ng/mL)	10.8 (34.2)[a]	14.2 (48.1)[b]
AUC_{inf} (h*ng/mL)	12.3 (33.9)[a]	16.1 (43.8)[b]
T_{max} (hours)	5.00 (5.00, 5.00)	4.00 (2.00, 4.00)
$t_{1/2}$ (hours)	13.1 (9.13, 17.8)[a]	17.3 (13.9, 20.8)[b]
T_{last} (hours)	36.0 (24.0, 48.0)	48.0 (36.0, 48.0)

[a] N=30; [b] N=26; %CV = percentage coefficient of variation; ROS = rosuvastatin; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2}$, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 1-9. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of TAF (25 mg) and its Metabolite, TFV, Following Administration Alone or with GS-6207 (N = 28-30)

Parameter	TAF Alone (N = 30)	TAF+ GS-6207 (Day 21; Co-administration) (N = 28)
TAF		
C_{max} (ng/mL)	248 (52.5)	322 (52.6)
AUC_{last} (h*ng/mL)	256 (54.3)	328 (35.3)
AUC_{inf} (h*ng/mL)	262 (54.4)[a]	361 (27.8)[b]
T_{max} (hours)	1.00 (0.50, 1.13)	1.00 (0.50, 1.50)
$t_{1/2}$ (hours)	0.38 (0.34, 0.42) [a]	0.41 (0.35, 0.43) [b]
TFV		
C_{max} (ng/mL)	6.29 (30)	7.97 (34.2)
AUC_{last} (h*ng/mL)	171 (26.3)	259 (22.2) [c]
AUC_{inf} (h*ng/mL)	206 (25.9)	322 (21)

%CV = percentage coefficient of variation; TAF = tenofovir alafenamide; TFV = tenofovir; Q1 = first quartile; Q3 = third quartile
a N=28
b N=22
c N=27
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 1-10. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of MDZ (2.5 mg) and its Metabolite, 1-OH-MDZ, Following Administration Alone or with GS-6207 (N = 30-31)

Parameter	MDZ Alone (N = 31)	MDZ+ GS-6207 (Day 24; Co-administration) (N = 30)	MDZ + GS-6207 (Day 25; 1 Day Post GS-6207 Dose) (N = 30)
MDZ			
C_{max} (ng/mL)	9.46 (29.1)	17.7 (22.7)	19.7 (23.8)
AUC_{last} (h*ng/mL)	50.5 (35.1)	129 (24.9)	171 (27.7)
AUC_{inf} (h*ng/mL)	52.9 (36.3)	170 (30.6)	208 (34.5)
T_{max} (hours)	2.00 (1.00, 2.00)	2.00 (1.25, 4.00)	2.00 (1.00, 2.00)
$t_{1/2}$ (hours)	5.18 (3.96, 7.2)	7.05 (6.06, 9.05)	9.38 (7.04, 11.4)
1-OH-MDZ			
C_{max} (ng/mL)	2.64 (44.4)	1.39 (34.9)	1.33 (36.5)
AUC_{last} (h*ng/mL)	13.1 (39.2)	8.12 (28.6)	9.7 (35.9)
AUC_{inf} (h*ng/mL)	13.9 (38.9)	9.56 (30)	11.5 (43)

%CV = percentage coefficient of variation; MDZ = midazolam; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

PIT AUC and C_{max} were not affected following administration with GS-6207, suggesting GS-6207 does not inhibit OATP transporters (Table 1-7). ROS AUC and C_{max} were approximately 1.3 to 1.6-fold higher following co-administration with GS-6207 (Table 1-8), suggesting GS-6207 inhibits BCRP transporters. TAF and TFV AUC and C_{max} were 1.2 to 1.6-fold higher following co-administration with GS-6207 (Table 1-9), suggesting GS-6207 is a weak inhibitor of P-gp transporters. MDZ AUC and C_{max} were approximately 2- to 4-fold higher, and 1-OH-MDZ AUC and C_{max} were correspondingly lower following co-administration with GS-6207 (Table 1-10), suggesting GS-6207 is a moderate inhibitor of CYP3A.

1.2.2.5. GS-US-200-4538

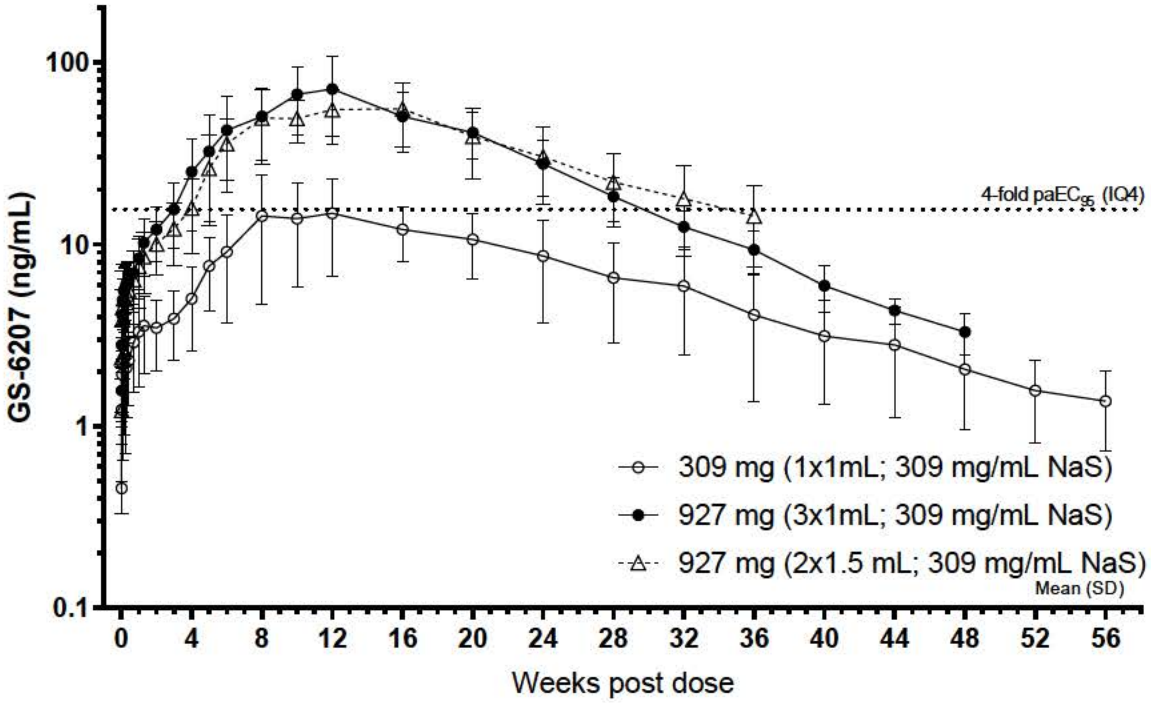
GS-US-200-4538 is an ongoing, blinded Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single ascending SC doses of GS-6207 solution formulations. As of 28 August 2019, 30 unique participants across 3 dosing cohorts have received single doses of either SC GS-6207 injection, 309 mg/mL or placebo (4:1 ratio). Analysis of other formulations is ongoing.

Based on the PK data available to date, the GS-6207 injection, 309 mg/mL was selected for use in this study. This formulation has been administered as single SC doses of either 309 mg (1 × 1.0 mL) or 927 mg (3 × 1.0 mL or 2 × 1.5 mL) in study GS-US-200-4538; these selected data are summarized below.

Pharmacokinetic Results

PK samples will be collected for up to 450 days; PK analysis is ongoing. Data available to date after administration of single doses of GS-6207 SC injection, 309 mg/mL are presented below (Figure 1-5, Table 1-11). Based on available PK data, a slow initial release of GS-6207 is observed; however, concentrations exceeding an IQ of 4 (4-fold higher than the paEC95 from MT-4 cells; 3.87 ng/mL) are observed for at least 26 weeks following a single 927 mg dose. Preliminary PK data through 20 weeks postdose suggest similar PK profiles following SC administration of a 927 mg dose administered as either 3 × 1.0 mL or 2 × 1.5 mL SC injections.

Figure 1-5. GS-US-200-4538: Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of GS-6207 Injection, 309 mg/mL (N = 8 per cohort)



paEC95= protein adjusted EC95 from MT-4 cells; 3.87 ng/mL

Table 1-11. Preliminary Pharmacokinetic Parameters for GS-6207 Injection, 309 mg/mL

PK parameter* (Mean %CV)	309 mg (1 × 1.0 mL) (N = 8)	927 mg (3 × 1.0 mL) N = 8	927 mg (2 × 1.5 mL) N = 8
AUC_{inf} (hr*ng/mL)	68700 (29.4)	256000 (28.8)	NC
AUC_{last} (hr*ng/mL)	49400 (28.8)	147000 (56.9)	NC
$\%AUC_{exp}$ (%)	28.6 (64.5)	30.3 (55.1)	NC
C_{max} (ng/mL)	17.7 (50.3)	67.0 (54.8)	NC
T_{max} (hr) [days]	2350 (1340, 3360) [98]	1850 (1680, 2020) [77]	NC
$T_{1/2}$ (hr) [days]	2550 (929, 3000) [106]	NC	NC

%CV = percentage coefficient of variation; NC = not calculated due to insufficient data at this time; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters presented to 3 significant figures as mean (%CV), except T_{max} and $T_{1/2}$: median (Q1, Q3).

Safety Results

In a preliminary blinded review of safety data as of 28 August 2019 of the 30 participants who received SC GS-6207 injection, 309 mg/mL, no deaths or Grade 4 AEs have been reported. One participant was hospitalized for SAE of Grade 3 abscess, which occurred at their ankle; it was considered not related to the study medication. No other serious or Grade 3 AEs have been reported.

The most frequently reported AEs were injection site induration (21 participants, 70.0%), injection site pain (14 participants, 46.7%), and headache and injection site erythema (both 10 participants, 33.3%). Adverse events reported for > 2 participants are presented in Table 1-12.

Overall, 7 of 30 participants (23.3%) had Grade 3 or 4 laboratory abnormalities. One participant had a Grade 4 creatine kinase elevation attributed to exercise.

No notable changes from predose in vital signs (systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiration rate) have been observed in the study. No clinically significant ECG abnormalities have been reported during the study.

Table 1-12. GS-US-200-4538: Summary of Adverse Events in > 2 Participants by Preferred Term

Preferred Term	GS-6207 309 mg / placebo N = 10	GS-6207 927 mg / placebo (3 × 1.0 mL) N = 10	GS-6207 927 mg / placebo (2 × 1.5 mL) N = 10	Total GS-6207 927 mg / placebo N = 20	Total N = 30
Number (%) of Participants with Any Treatment-Emergent AE	7 (70%)	10 (100)	10 (100)	20 (100)	27 (90)
Injection site induration	3 (30)	8 (80)	10 (100)	18 (90)	21 (70)
Injection site pain	-	6 (60)	8 (80)	14 (70)	14 (47)
Headache	3 (30)	4 (40)	3 (30)	7 (35)	10 (33)
Injection site erythema	1 (10)	5 (50)	4 (40)	9 (45)	10 (33)
Injection site swelling	-	4 (40)	4 (40)	8 (40)	8 (27)
Injection site nodule	2 (20)	3 (30)	-	3 (14)	5 (17)
Injection site bruising	-	3 (30)	1 (10)	4 (20)	4 (13)
Upper respiratory tract injection	1 (10)	1 (10)	1 (10)	2 (10)	3 (10)

AE = adverse event

1.2.2.6. GS-US-200-5709

GS-US-200-5709 is an ongoing Phase 1, open-label, multiple-cohort study in healthy participants assessing the safety, tolerability, and PK of multiple-dose oral (tablet) and SC (309 mg/mL NaS) GS-6207.

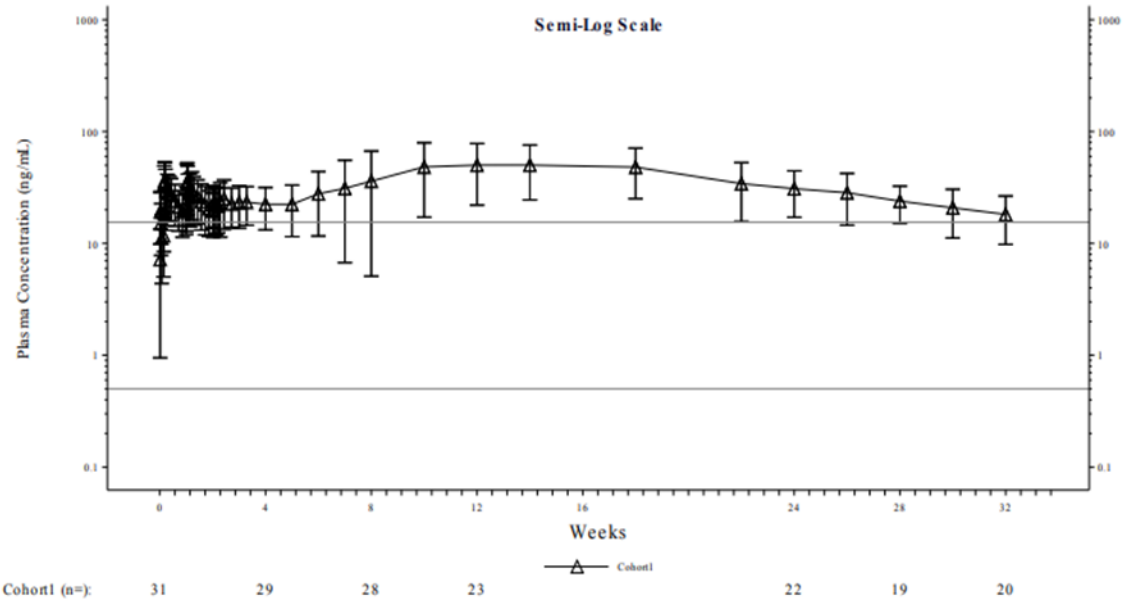
In Cohorts 1 and 2 of this study, safety and PK of potential clinical regimens will be evaluated. Study conduct is ongoing.

Cohort 3 of this study characterized the safety and PK of GS-6207 administered at clinically relevant therapeutic and supratherapeutic exposures; this regimen included oral GS-6207 600 mg administered twice daily for 11 days, with the last dose given in the morning on the 11th day.

Preliminary Pharmacokinetic Results

Interim PK data through Day 225 for Cohort 1 after administration of oral GS-6207 600 mg on Days 1 and 2, oral GS-6207 300 mg on Day 8, and SC GS-6207 927 mg on Day 15, are presented in Figure 1-6. Intensive PK sampling was conducted on Days 1, 2, 8, and 15, and single anytime PK samples were collected at prespecified study visits through Day 225. The GS-6207 PK parameters for Days 1, 2, 8, and 15 are summarized in Table 1-13. Mean GS-6207 plasma concentrations and their lower bound 90% CIs achieved IQ4 (4-fold higher than $paEC_{95}$) within 2 hours postdose on Day 2, and this was maintained through Week 30.

Figure 1-6. GS-US-200-5709: Mean (SD) GS-6207 Plasma Concentration Versus Time (Cohort 1: Through Day 225) (GS-6207 PK Analysis Set)



BLQ = below the limit of quantitation; IQ4 = inhibitory quotient of 4; GS-6207 = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SC = subcutaneous; SD = standard deviation
Cohort 1 dosing was oral GS-6207 600 mg on Days 1 and 2, oral GS-6207 300 mg on Day 8, and SC GS-6207 927 mg on Day 15.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ was defined as 0.5 ng/mL for GS-6207.
Postdose concentration values ≤ LLOQ were not presented on the figure.
Figures on the semi-log scale were set to include all lower bar and mean/median values > 0 on the Y-axis.
Reference lines indicate IQ4 (15.5 ng/mL) and LLOQ (0.5 ng/mL)

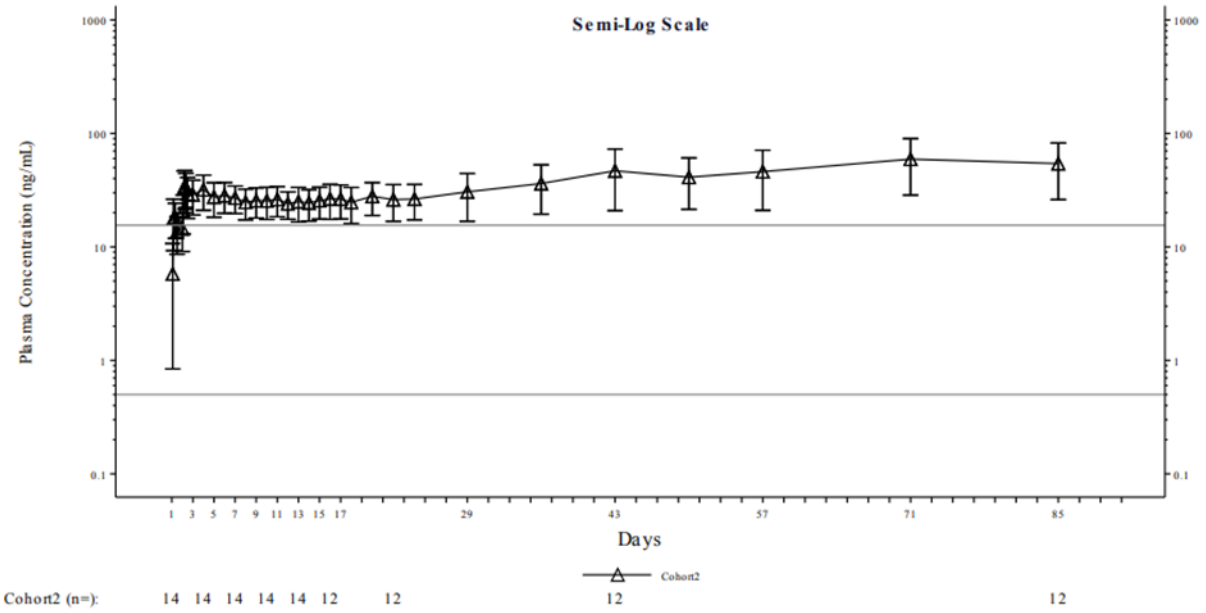
Table 1-13. GS-US-200-5709: Summary Statistics of GS-6207 Plasma Pharmacokinetic Parameters (Cohort 1) (GS-6207 PK Analysis Set)

PK Parameter Mean (%CV)	GS-6207			
	Day 1 600 mg oral GS-6207 (2 × 300 mg tablets) (N = 31)	Day 2 600 mg oral GS-6207 (2 × 300 mg tablets) (N = 31)	Day 8 300 mg oral GS-6207 (1 × 300 mg tablet) (N = 31)	Day 15 927 mg SC GS-6207 (2 × 1.5 mL 309 mg/mL NaS) (N = 30)
C_{max} (ng/mL)	22.0 (45.5)	40.4 (43.4)	39.3 (44.7)	58.7 (58.1)
T_{max} (h)[a] [days]	4.00 (4.00, 6.00) [0.17]	6.00 (4.00, 8.00) [0.25]	6.00 (4.00, 8.00) [0.25]	2028.04 (1682.45, 2688.23) [84.5]
C_{last} (ng/mL)	11.2 (60.8)	19.2 (40.8)	20.6 (43.1)	25.0 (81.7)
T_{last} (h)[a] [days]	12.00 (12.00, 12.00) [0.5]	120.00 (120.00, 120.00) [5.0]	144.00 (144.00, 144.00) [6.0]	5037.95 (4032.00, 5042.33) [209.9]

%CV = percentage coefficient of variation; BLQ = below the limit of quantitation; GS-6207 = lenacapavir; LLOQ = lower limit of quantitation; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Median (Q1, Q3).
Values BLQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ was defined as 0.5 ng/mL for GS-6207.

Interim PK data through Day 85 for Cohort 2 after administration of SC GS-6207 927 mg and oral GS-6207 600 mg on Day 1, followed by oral GS-6207 600 mg on Day 2, are presented in Figure 1-7. Intensive PK sampling was conducted on Days 1 and 2, and single anytime PK samples were collected at prespecified study visits through Day 85. The GS-6207 PK parameters for Days 1 and 2 are summarized in Table 1-14. Mean GS-6207 plasma concentrations and their lower bound 90% CIs achieved IQ4 within 2 hours postdose on Day 2, and this was maintained through Day 85. From Days 0 to 85, mean $AUC_{0\text{-}85d}$ (%CV) of 83,082.9 h•ng/mL (43.6%), was generally comparable to Cohort 1 (68,364.8 h•ng/mL [49.8%]).

Figure 1-7. GS-US-200-5709: Mean (SD) GS-6207 Plasma Concentration Versus Time (Cohort 2: Through Day 85) (GS-6207 PK Analysis Set)



BLQ = below the limit of quantitation; IQ4 = inhibitory quotient of 4; GS-6207 = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SC = subcutaneous; SD = standard deviation
Cohort 2 dosing was SC GS-6207 927 mg and oral GS-6207 600 mg on Day 1 and oral GS-6207 600 mg on Day 2.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ was defined as 0.5 ng/mL for GS-6207.
Postdose concentration values ≤ LLOQ were not presented on the figure.
Figures on the semi-log scale were set to include all lower bar and mean/median values > 0 on the Y-axis.
Reference lines indicate IQ4 (15.5 ng/mL) and LLOQ (0.5 ng/mL)

Table 1-14. GS-US-200-5709: Summary Statistics of GS-6207 Plasma Pharmacokinetic Parameters (Cohort 2) (GS-6207 PK Analysis Set)

PK Parameter Mean (%CV)	GS-6207	
	Day 1 927 mg SC GS-6207 (2 × 1.5 mL 309 mg/mL NaS) 600 mg Oral GS-6207 (2 × 300 mg Tablets) (N = 14)	**Day 2 600 mg Oral GS-6207 (2 × 300 mg Tablets) (N = 14)**
C_{max} (ng/mL)	19.9 (35.5)	64.7 (45.0)
T_{max} (h)[a] [days]	6.00 (4.00, 8.00) [0.25]	1653.74 (12.00, 1653.98) [68.9]
C_{last} (ng/mL)	13.6 (36.5)	53.8 (54.2)
T_{last} (h)[a] [days]	12.0 (12.0, 12.0) [0.50]	1991.16 (1990.70, 1991.18) [83.0]

%CV = percentage coefficient of variation; BLQ = below the limit of quantitation; GS-6207 = lenacapavir; LLOQ = lower limit of quantitation; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Median (Q1, Q3).
Values BLQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ was defined as 0.5 ng/mL for GS-6207.

Final PK data from Cohort 3 after administration of oral GS-6207 600 mg twice daily (Days 1 through 10), followed by an oral GS-6207 600 mg dose in the morning on Day 11, are presented in Table 1-15. Intensive PK sampling (from 0 to 12 hours) was conducted on Days 1, 2, and 11 with sparse sampling on Days 3, 4, 8, 9, and 10. As shown, GS-6207 exhibited significant accumulation over the course of 11 days of dosing, which is consistent with its long $t_{1/2}$.

Table 1-15. GS-US-200-5709: Summary Statistics of GS-6207 Plasma Pharmacokinetic Parameters (Cohort 3) (GS-6207 PK Analysis Set)

PK Parameter Mean (%CV)	GS-6207							
	600 mg oral GS-6207 (2 × 300 mg tablets; AM dose) and 600 mg oral GS-6207 (2 × 300 mg tablets; PM dose)							600 mg oral GS-6207 (2 × 300 mg tablets; AM dose)
	Day 1 (N = 15)	Day 2 (N = 15)	Day 3 (N = 15)	Day 4 (N = 15)	Day 8 (N = 15)	Day 9 (N = 15)	Day 10 (N = 15)	Day 11 (N = 15)
$AUC_{0\text{-}12h}$ (h•ng/mL)	135.4 (30.7)	894.4 (47.2)	NC	NC	NC	NC	NC	9706.9 (28.2)
C_{max} (ng/mL)	19.0 (24.0)	96.4 (49.5)	NC	NC	NC	NC	NC	1012.1 (26.2)
T_{max} (h)[a]	5.00 (4.00, 5.00)	8.00 (5.00, 11.97)	NC	NC	NC	NC	NC	4.00 (4.00, 5.00)
C_{last} (ng/mL)	11.1 (39.9)	88.4 (45.2)	241.6 (41.2)	376.9 (31.7)	604.8 (32.6)	680.5 (28.2)	751.9 (25.7)	787.7 (31.3)
T_{last} (h)[a]	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)
C_0 (ng/mL)	BLQ (BLQ)	42.0 (47.2)	152.6 (49.7)	342.4 (39.6)	558.5 (36.8)	699.9 (33.2)	693.1 (35.0)	788.8 (32.1)

BLQ = below the limit of quantitation; %CV = percentage coefficient of variation; GS-6207 = lenacapavir; LLOQ = lower limit of quantitation; NC = not calculated due to insufficient PK sampling; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile

a Median (Q1, Q3).

C_0 represents concentration at time 0 hours.

Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.

LLOQ was defined as 0.5 ng/mL for GS-6207.

Preliminary Safety Results

Interim safety data through 25 June 2021 for Cohorts 1 and 2 and final safety data for Cohort 3 are summarized below.

A total of 31 participants were enrolled into Cohort 1 and received at least 1 dose of study drug. Overall, GS-6207 was generally safe and well tolerated. No Grade 3 or 4 AEs, SAEs, deaths, or pregnancies were reported. One participant (3.2%) prematurely discontinued study drug and the study due to a Grade 1 AE of SARS-CoV-2 test positive. Five participants (16.1%) had Grade 3 laboratory abnormalities (increased fasting triglycerides [2 participants] and increases in

creatinine kinase (CK), fasting urine glucose, and fasting creatinine [1 participant each]), and 1 participant (3.2%) had a Grade 4 laboratory abnormality (increased fasting triglycerides).

A total of 14 participants were enrolled into Cohort 2 and received at least 1 dose of study drug. Overall, GS-6207 was generally safe and well tolerated. No Grade 3 or 4 AEs, SAEs, AEs leading to study drug or study discontinuation, deaths, or pregnancies were reported. No participant had Grade 4 laboratory abnormalities. Three participants (21.4%) had Grade 3 laboratory abnormalities (increased fasting cholesterol and LDL cholesterol [1 participant] and increases in CK and fasting triglycerides [1 participant each]).

No participant in Cohort 1 or 2 had notable changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse, and temperature) or clinically significant electrocardiogram (ECG) abnormalities.

A total of 15 participants were enrolled in Cohort 3 and completed GS-6207 600 mg twice daily dosing for 11 days, with the last dose given in the morning on the 11th day. Overall, GS-6207 was generally safe and well tolerated at clinically relevant therapeutic and supratherapeutic exposures. Despite the supratherapeutic exposures observed, no Grade 3 or 4 AEs, SAEs, AEs leading to study drug or study discontinuation, deaths, or pregnancies were reported. One participant (6.7%) experienced an AE of dyspepsia (Grade 1), which was not considered related to study drug. No participant had Grade 4 laboratory abnormalities. One participant (6.7%) had Grade 3 increased fasting triglycerides. No participant had notable changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse, and temperature) or clinically significant ECG abnormalities. Specifically, no participant had postbaseline QTcF exceeding 450 milliseconds.

1.2.2.7. GS-US-200-4625

Study GS-US-200-4625 is a Phase 2/3, placebo-controlled, multicenter study of GS-6207 together with an optimized background regimen (OBR) in heavily treatment-experienced (HTE) people with HIV-1 (PWH) with multidrug resistant infection.

Herein is a summary from the 2 clinical study reports of interim analysis at Week 26 (after all participants in Cohort 1 completed the Week 26 visit) and the Week 52 addendum (after all participants in Cohort 1 completed the Week 26 visit and all participants in Cohort 2 completed Week 26 visit).

Participants in Cohort 1 were randomized to receive either oral GS-6207 or placebo, while also continuing their failing regimen during a 14-day Functional Monotherapy Period. After this period, participants who received oral GS-6207 switched to SC GS-6207 (972 mg; 309 mg/mL; 2 × 1.5 mL) and OBR, and participants who had received placebo then received oral GS-6207 and OBR for 14 days prior to switching to SC GS-6207 (972 mg; 309 mg/mL; 2 × 1.5 mL) and OBR. Participants in Cohort 2 received oral GS-6207 and OBR for 14 days before switching to SC GS-6207 and OBR. Cohort 2 includes participants that did not meet the criteria for randomization in Cohort 1 or who joined the study after Cohort 1 was fully enrolled.

Disposition and Baseline Characteristics

Overall in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: GS-6207, 24 participants; placebo, 12 participants; Cohort 2: GS-6207 + OBR, 36 participants). All 72 participants completed the Functional Monotherapy (Cohort 1, 36 participants) or oral Lead-in Period (Cohort 2, 36 participants), and all received Day 1 SC GS-6207.

Of the 72 participants who received Day 1 SC GS-6207, 32 participants (all from Cohort 2) are continuing study drug in the Main Phase, and 37 participants completed study drug in the Main Phase (Week 52). Three participants discontinued study drug during the Main Phase. Reasons for premature discontinuation were lost to follow-up, investigator's discretion, and death (1 participant each, 1.4%). One participant who decided not to receive SC GS-6207 at Week 52 and not to continue the study completed the study at the Week 52 visit. Thirty-six participants entered into the Extension Phase (Cohort 1: 34 participants; Cohort 2: 2 participants). Of the 36 participants who entered the Extension Phase, 34 participants are continuing study drug. Two participants discontinued study drug during the Extension Phase. Reasons for premature discontinuation were AE and lost to follow-up (1 participant each, 2.8%).

Cohort 1

In Cohort 1, demographic and baseline characteristics were generally similar between the GS-6207 and placebo groups. The majority of participants were male (72.2%; 26 of 36 participants), White (45.7%, 16 participants) or Black (45.7%, 16 participants), and not Hispanic or Latino (71.4%, 25 participants). Median age was 54 years (range: 24−71 years).

Baseline disease characteristics were consistent with the profile of the HTE population, with a median (range) number of prior ARV medications of 9 (2, 24), and 75% of participants with CD4 cell count < 200 cells/μL (a hallmark of severe immune suppression and the criterion to diagnose AIDS). Differences were seen between the GS-6207 and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage.

The most common prior ARV medications were as follows: INSTI (97.2%), NRTI (94.4%), nonnucleoside reverse transcriptase inhibitor (NNRTI; (88.9%), and protease inhibitor (PI; (83.3%). Known resistance to ≥ 2 drugs in class was as follows: NRTI (97.2%), NNRTI (94.4%), PI (77.8%), and INSTI (75.0%).

The median number of ARVs in the failing regimen for Cohort 1 was 3 (range: 1−7). The composition of participants' failing regimens were characteristic of those of PWH with multidrug resistance, for example, PI (boosted darunavir twice daily), INSTI (dolutegravir twice daily), chemokine receptor 5 entry inhibitor (maraviroc), CD4-directed post attachment (ibalizumab), attachment inhibitor (fostemsavir, which was investigational at the time of enrollment), and fusion inhibitor (enfuvirtide).

The median number of ARVs in the OBR was 4 (range: 2−7). The composition of participants' failing regimens and OBRs were similar, suggesting that they had few remaining treatment options prior to enrolling. Specifically, 6 out of 36 (16.7%) of participants continued their failing regimens as OBRs, suggesting there were no viable agents that could have further optimized the regimen.

The percentage of participants by number of fully active ARV agents in the OBR were as follows: 16.7% (0 fully active ARV agents), 38.9% (1 fully active ARV agent), 25.0% (2 fully active ARV agents), and 19.4% (≥ 3 fully active ARV agents).

Cohort 2

In Cohort 2, the majority of participants were male (77.8%; 28 of 36 participants), White (36.1%, 13 participants) or Asian (33.3%, 12 participants), and not Hispanic or Latino (86.1%, 31 participants). Median age was 49 years (range: 23−78 years).

The baseline disease characteristics, prior ARVs, failing regimens, OBR regimen, and resistance characteristics for Cohort 2 were consistent with the profile of the HTE population.

Efficacy Results:

Primary efficacy end point: Reduction in HIV 1 RNA of ≥ 0.5 $\log_{10}$ copies/mL

A significantly greater percentage of participants receiving GS-6207 had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period compared than those receiving placebo (87.5% vs 16.7%; $P < 0.0001$). To address the imbalance in baseline HIV-1 RNA between the GS-6207 and placebo groups, a post hoc analysis of the primary efficacy end point with adjustment for baseline HIV-1 RNA using rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant: 87.5% versus 16.7%; $P = 0.0003$. To address the imbalance in baseline CD4 cell count between the GS-6207 and placebo groups, post hoc analyses of the primary efficacy end point were conducted in participants with comparable or clinically relevant CD4 cell counts. These analyses showed that the difference between groups remained statistically significant for the comparison between participants in the GS-6207 group with a low baseline CD4 cell count (median: 98.5 cells/μL; n = 12) and participants in the placebo group (median: 84.5 cells/μL; n = 12) ($P = 0.0008$) and between participants in the GS-6207 and placebo groups with a baseline CD4 cell count < 200 cells/μL ($P < 0.0001$).

Secondary Efficacy End Points

Week 26

The percentages of participants in Cohort 1 with HIV 1 RNA < 50 and < 200 copies/mL at Week 26 using the United States (US) Food and Drug Administration (FDA) defined snapshot algorithm were 80.6% (29 of 36 participants) and 88.9% (32 of 36 participants), respectively. The percentages of participants in Cohort 2 with HIV 1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA defined snapshot algorithm were 66.7% (4 of 6 participants) and 66.7% (4 of 6 participants), respectively.

Week 52

The percentages of participants in Cohort 1 with HIV 1 RNA < 50 and < 200 copies/mL at Week 52 using the US FDA defined snapshot algorithm were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively.

HIV-1 RNA < 50 Copies/mL and < 200 Copies/mL

At Week 26, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 80.6% (58 of 72 participants) and 87.5% (63 of 72 participants), respectively.

At Week 52, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants), respectively.

Change From Baseline in HIV-1 RNA

Mean (SD) baseline HIV-1 RNA values of participants in Cohorts 1 and 2 was 4.12 (1.028) $\log_{10}$ copies/mL. The mean (SD) change from baseline in HIV-1 RNA at Weeks 26 and 52 was −2.53 (1.184) $\log_{10}$ copies/mL, and −2.50 (1.145) $\log_{10}$ copies/mL, respectively.

Change From Baseline in CD4 Cell Count

Mean (SD) baseline CD4 cell count value of participants in Cohorts 1 and 2 at baseline was 212 (226.2) cells/µL. At Week 26, mean (SD) change from baseline was 89 (106.7) cells/µL. At Week 52, mean (SD) change from baseline was 94 (121.5) cells/µL.

Preliminary Pharmacokinetic Results

A population PK (PopPK) model was developed from multiple Phase 1/2 studies to simultaneously describe IV, oral, and SC routes of administration for the GS-6207 treatment program. Data from Study GS-US-200-4625 up to Week 13 (interim PK data cut) were utilized in the PopPK model to derive posthoc exposure parameters. Following a dosing schedule of GS-6207 SC (927 mg or 2 x 1.5 mL of 309 mg/mL, administered every 26 weeks), preceded by a

14-day oral Lead-in Period, mean (%CV) GS-6207 post hoc C_{max} and C_{Week26} were 136.2 (75.2) ng/mL and 35.1 (59.2) ng/mL, respectively.

Adverse Events

Functional Monotherapy Period

During the Functional Monotherapy Period, the percentages of participants who experienced AEs were: GS-6207 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants). Nausea was the only AE reported in > 1 participant (GS-6207 12.5%, 3 participants).

Adverse event considered related to study drugs that was reported in > 1 participant was as follows: nausea (8.3%, 2 participants; GS-6207 group).

No deaths, SAEs, AEs leading to discontinuation of study drug, or Grade 3 or higher AEs, were reported in either the GS-6207 or placebo group.

All GS-6207 Analysis

The percentage of participants who received GS-6207 in Cohorts 1 and 2 and experienced AEs was 93.1% (67 of 72 participants). The 3 most commonly reported AEs were injection site pain (37.5%, 27 of 72 participants), injection site swelling (33.3%, 24 participants), and injection site erythema (27.8%, 20 participants). Some injection site reactions (ISRs) were attributed to enfuvirtide.

The majority of AEs were Grade 1 or 2 in severity. Grade 3 or higher AEs were reported for 16 participants (22.2%). Grade 3 or higher AEs that were reported for ≥ 2 participants were injection site erythema (5.6%, 4 participants), injection site edema, injection site pain, and injection site swelling (2.8%, 2 participants each). Four participants experienced Grade 3 or higher AEs that were considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and immune reconstitution inflammatory syndrome (1 participant each). The AE of abdominal abscess was an abscess at the injection site due to secondary infection most likely because the participant scratched the injection site.

Overall, 66.7% (48 of 72 participants) experienced treatment-related AEs. The most commonly reported treatment-related AEs were injection site pain and injection site swelling (30.6%, 22 participants), injection site erythema (25.0%, 18 participants), and injection site nodule (23.6%, 17 participants)

SAEs were reported for 11.1% (8 of 72 participants). The only SAE that was reported for more than 1 participant was COVID-19. None of these events led to discontinuation of study drug. No SAEs were considered related to study drug. One SAE of cancer resulted in death which was also reported as an AE leading to premature discontinuation from the study. This participant in Cohort 2 died on Study Day 90, and the cause of death was reported as cancer. The event was previously reported in the Week 26 analysis and was considered not related to study drug.

While no participant discontinued study drug due to AE at the Week 26 analysis, 1 participant (1.4%) in Cohort 1 experienced a Grade 1 AE of injection site nodule during the Extension Phase, leading to premature discontinuation from the study after receiving the Week 52 GS-6207 SC injection. The event was considered related to study drug.

Overall, 45 participants (62.5%) experienced a study drug-related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR which resolved after a few days. No Grade 3 or 4 ISRs were reported beyond Week 26. The median (Q1, Q3) total duration of any study drug-related ISR was 8 (3, 67) days. The most frequently reported study drug-related ISRs (reported in ≥ 10% of participants overall) and duration in median (Q1, Q3) days were as follows:

- Injection site swelling (30.6%, 22 participants), 12 (6, 30) days
- Injection site pain (30.6%, 22 participants), 3 (2, 7) days
- Injection site nodule (23.6%, 17 participants), 180 (111, 330) days
- Injection site erythema (25%, 18 participants), 6 (3, 8) days
- Injection site induration (15.3%, 11 participants), 118 (15, 182) days

A numerically lower percentage of participants had ISRs after the second GS-6207 injection compared with the first injection.

Overall, 17 participants experienced study drug-related injection site nodule, and 11 participants experienced study drug-related injection site induration. All events were Grade 1 or 2.

The injection site nodules and indurations reported due to Day 1 SC injection were as follows:

- Participant level analysis:
  - Nodules: Ongoing (9/16 [56.3%]); Resolved (7/16 [43.8%])
  - Indurations: Ongoing (1/8 [12.5%]); Resolved (7/8 [87.5%])
- Event level analysis:
  - Nodules: Ongoing (9/23 [39.1%]); Resolved (14/23 [60.9%])
  - Indurations: Ongoing (1/8 [12.5%]); Resolved (7/8 [87.5%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to Day 1 SC injection was 107 (70, 227) days and 43 (15, 196) days, respectively.

The injection site nodules and indurations reported due to the second GS-6207 injection at Week 26 were as follows:

- Participant level analysis:
  - Nodules: Ongoing (6/8 [75.0%%]); Resolved (2/8 [25.0%])
  - Indurations: Ongoing (3/7 [42.9%]); Resolved (4/7 [57.1%])
- Event level analysis:
  - Nodules: Ongoing (12/14 [85.7%]); Resolved (2/14 [14.3%])
  - Indurations: Ongoing (3/7 [42.9%]); Resolved (4/7 [57.1%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to the second GS-6207 injection at Week 26 was 92 (3, 180) Days and 38 (9, 123) Days, respectively.

CONCLUSIONS:

The conclusions from the Week 52 interim analysis of Study GS-US-200-4625 are as follows:

- Consistent with the data reported in the Study GS-US-200-4625 Interim Week 26 CSR, high rates of virologic suppression continued to be maintained through Week 52. These results were consistent even in participants who had suboptimal baseline OBR (eg, low OSS, no or 1 fully active agent, INSTI resistance, no dolutegravir or darunavir), demonstrating a clinically meaningful contribution of GS-6207 towards virologic suppression.
- Consistent with the data reported in the Study GS-US-200-4625 Interim Week 26 CSR, there were clinically meaningful increases in CD4 cell count from baseline to Week 52.

GS-6207 remained generally safe and well tolerated. No participant experienced a study drug-related SAE. The majority of ISRs were Grade 1 or 2 in severity. One participant discontinued GS-6207 at Week 52 (after the Week 26 interim analysis) due to an AE of Grade 1 injection site nodule.

1.2.2.8. GS-US-200-4334

Study GS-US-200-4334 is an ongoing, Phase 2, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of GS-6207 in combination with other ARV agents in ARV-naive PWH. Participants were randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups (Table 1-16, Figure 1-8).

Participants are treated for at least 80 weeks. Participants in Treatment Group 4 will complete the study at Week 80.

Herein is a summary from the two clinical study reports of interim analysis at Week 28 and the Week 54 addendum.

Table 1-16. GS-US-200-4334: Study Treatments

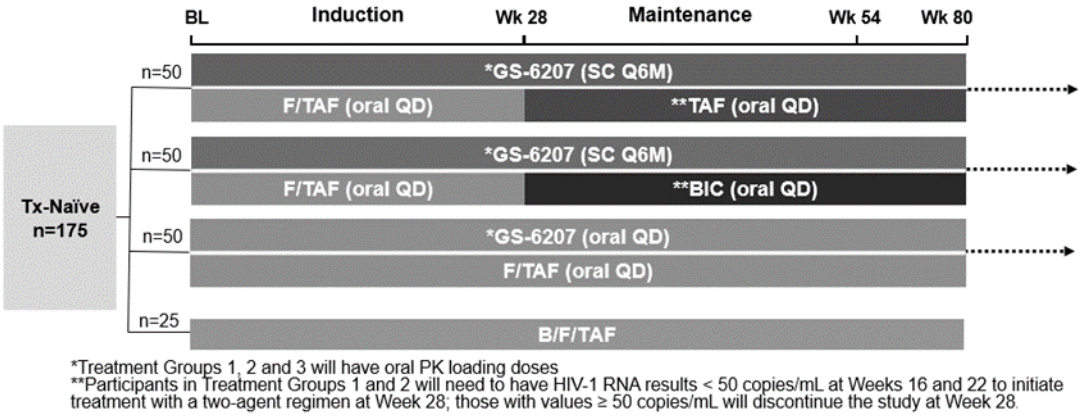
Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	• Oral GS-6207 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 • Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC GS-6207 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	• SC GS-6207 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter • Oral daily TAF (25 mg)
2	Induction (Day 1 through Week 27)	• Oral GS-6207 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 • Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[b] • SC GS-6207 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	• SC GS-6207 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter • Oral daily BIC (75 mg)
3	Day 1 through Week 80	• Oral GS-6207 600 mg (2 × 300 mg tablet) on Days 1 and 2; 50 mg (1 × 50 mg tablet) daily from Day 3 onwards • Oral daily F/TAF (200/25 mg)
4	Day 1 through Week 80	• Oral daily B/F/TAF (50/200/25 mg)

BIC, B = bictegravir; F = emtricitabine; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); GS-6207 = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

a Treatment Group 1 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily TAF.

b Treatment Group 2 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily BIC.

Figure 1-8. GS-US-200-4334: Study Design



BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®, BVY); BL = baseline; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); GS-6207 = lenacapavir, LEN; PK = pharmacokinetic; QD = once daily; Q6M = every 6 months; SC = subcutaneous; TAF = tenofovir alafenamide; Tx-naive = treatment naive; Wk = week

Disposition and Baseline Characteristics

Of the 249 participants screened, 183 were randomized, and 182 received at least 1 dose of study drug. Of these 182 participants, 22 participants (12.1%) prematurely discontinued the study drug during the Main Phase (ie, data collected on or before Week 80): 17 of 105 participants (16.2%) in the SC GS-6207 total group, 4 of 52 participants (7.7%) in the oral GS-6207 group, and 1 of 25 participants (4.0%) in the bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®; BVY) group. The reasons for premature study drug discontinuation in the SC GS-6207 total group were participant decision and lost to follow-up (each 4 participants [3.8%]), investigator's discretion, lack of efficacy, and AE (each 3 participants [2.9%]). The reasons for premature study drug discontinuation in the oral GS-6207 group were lost to follow-up (3 participants [5.8%]) and participant decision (1 participant [1.9%]) and in the BVY group it was participant decision (1 participant [4.0%]).

As of the Week 54 data cut date, 8 participants entered into the Extension Phase (SC GS-6207 total group, 5 participants; oral GS-6207 group, 3 participants) and were continuing study drug.

Demographics, general baseline characteristics, and baseline disease characteristics are described in the Interim Week 28 CSR.

Demographic and baseline characteristics were similar across the treatment groups. Most participants were male (93.4%), cisgender (92.3%), and gay (69.8%). Median age was 29 years (range: 19−72 years). Race was balanced between Black versus non-Black (52.2% vs 47.8%, respectively), as was ethnicity between Hispanic or Latino versus not Hispanic or Latino (45.1% vs 54.9%, respectively).

Baseline disease characteristics were similar across the treatment groups. Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.37 (3.86, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) baseline CD4 cell count was 437 (332, 599) cells/μL. Among the 182 participants, most had HIV-1 RNA ≤ 100,000 copies/mL (85.2%, 155 participants) and a CD4 cell count range of ≥ 350 to < 500 cells/μL (31.9%, 58 participants) or ≥ 500 cells/μL (37.4%, 68 participants).

Efficacy Results:

Primary Efficacy End Point

HIV-1 RNA < 50 copies/mL at Week 54 Using the US FDA-Defined Snapshot Algorithm

The primary analysis at Week 54 demonstrated similar results in each treatment group, with no significant difference between each of the GS-6207-containing groups and the BVY group, as follows:

- GS-6207 total: 136 of 157 participants (86.6%)
- SC GS-6207 + (DVY → TAF): 47 of 52 participants (90.4%)
- SC GS-6207 + (DVY → BIC): 45 of 53 participants (84.9%)
- Oral GS-6207 + DVY: 44 of 52 participants (84.6%)
- BVY: 23 of 25 participants (92.0%)

For participants with HIV-1 RNA < 50 copies/mL at Week 28, the proportion with HIV-1 RNA < 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm were also similar in each treatment group, with no significant difference between each of the GS-6207-containing groups and the BVY group, as follows:

- GS-6207 total: 135 of 147 participants (91.8%)
- SC GS-6207 + (DVY → TAF): 46 of 49 participants (93.9%)
- SC GS-6207 + (DVY → BIC): 45 of 49 participants (91.8%)
- Oral GS-6207 + DVY: 44 of 49 participants (89.8%)
- BVY: 23 of 25 participants (92.0%)

Secondary Efficacy End Points

Week 28

Results from the secondary efficacy analysis of Week 28 data of Study GS-US-200-4334 demonstrated similar results in each treatment group, with no significant difference between each of the GS-6207-containing treatment groups and the BVY treatment group with respect to the proportion of participants with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm, the change from baseline in $\log_{10}$ HIV-1 RNA, and the change from baseline in CD4 cell count.

HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm

- GS-6207 total: 147 of 157 participants (93.6%)
- SC GS-6207 + (DVY → TAF): 49 of 52 participants (94.2%)
- SC GS-6207 + (DVY → BIC): 49 of 53 participants (92.5%)
- Oral GS-6207 + DVY: 49 of 52 participants (94.2%)
- BVY: 25 of 25 participants (100.0%)

Week 38

HIV-1 RNA < 50 copies/mL at Week 38 Using the US FDA-defined snapshot algorithm

- GS-6207 total: 140 of 157 participants (89.2%)
- SC GS-6207 + (DVY → TAF): 47 of 52 participants (90.4%)
- SC GS-6207 + (DVY → BIC): 47 of 53 participants (88.7%)
- Oral GS-6207 + DVY: 46 of 52 participants (88.5%)
- BVY: 24 of 25 participants (96.0%)

Change from Baseline in HIV-1 RNA at Weeks 28, 38 and 54

Week 28

- GS-6207 total: −2.99 (0.666) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → TAF): −2.92 (0.649) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → BIC): −3.04 (0.638) $\log_{10}$ copies/mL

- Oral GS-6207 + DVY: −3.01 (0.716) $\log_{10}$ copies/mL

Week 38

- GS-6207 total: −3.01 (0.681) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → TAF): −2.96 (0.639) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → BIC): −3.06 (0.641) $\log_{10}$ copies/mL
- Oral GS-6207 + DVY: −3.02 (0.771) $\log_{10}$ copies/mL
- BVY: −3.04 (0.760) $\log_{10}$ copies/mL

Week 54

- GS-6207 total: −2.98 (0.700) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → TAF): −2.95 (0.636) $\log_{10}$ copies/mL
- SC GS-6207 + (DVY → BIC): −3.12 (0.589) $\log_{10}$ copies/mL
- Oral GS-6207 + DVY: −2.85 (0.840) $\log_{10}$ copies/mL
- BVY: −3.08 (0.787) $\log_{10}$ copies/mL

Change from Baseline in CD4 Cell Count at Weeks 38 and 54

Week 28

- GS-6207 total: 179 (166.0) cells/μL
- SC GS-6207 + (DVY → TAF): 172 (178.2) cells/μL
- SC GS-6207 + (DVY → BIC): 158 (164.1) cells/μL
- Oral GS-6207 + DVY: 206 (154.6) cells/μL
- BVY: 163 (157.7) cells/μL

Week 38

- GS-6207 total: 208 (172.7) cells/μL
- SC GS-6207 + (DVY → TAF): 195 (164.6) cells/μL
- SC GS-6207 + (DVY → BIC): 219 (187.4) cells/μL

- Oral GS-6207 + DVY: 210 (167.1) cells/μL
- BVY: 232 (209.3) cells/μL

Week 54

- GS-6207 total: 213 (182.1) cells/μL
- SC GS-6207 + (DVY → TAF): 206 (187.0) cells/μL
- SC GS-6207 + (DVY → BIC): 212 (187.1) cells/μL
- Oral GS-6207 + DVY: 220 (175.5) cells/μL
- BVY: 193 (191.1) cells/μL

Results from the secondary efficacy analysis at Weeks 38 and 54 demonstrated similar results in each treatment group, with no significant difference between each of the GS-6207-containing treatment groups and the BVY treatment group with respect to the proportion of participants with HIV-1 RNA < 50 copies/mL (Week 38), the change from baseline in $\log_{10}$ HIV-1 RNA, and the change from baseline in CD4 cell count (Weeks 38 and 54).

Preliminary Pharmacokinetic Results

As per the PopPK modeling summarized in Section 1.2.2.7, the mean (%CV) GS-6207 post hoc C_{max} and C_{Week26} in Study GS-US-200-4334 were 93.1 (61.9) ng/mL and 22.5 (63.4) ng/mL, respectively.

Safety Results:

GS-6207 and BVY were well tolerated. By Week 54, 89.2% of participants in the GS-6207 total group (140 of 157 participants) and 96.0% of those in the BVY group (24 of 25 participants) had been exposed to study drug for at least 54 weeks.

Adverse Events

Similar percentages of participants in the GS-6207 total (total of 157 participants) and BVY (total of 25 participants) groups had any AE by Week 54 (GS-6207 total 87.9%, 138 participants; BVY 84.0%, 21 participants).

The most commonly reported AEs were as follows:

- GS-6207 total (157 participants), excluding ISRs: headache and nausea (each 13.4%, 21 participants), COVID-19 (9.6%, 15 participants), and syphilis and lymphadenopathy (each 8.9%, 14 participants)

- SC GS-6207 total (105 participants), only ISRs: injection site erythema (31.4%, 33 participants), injection site swelling (27.6%, 29 participants), and injection site pain (23.8%, 25 participants)

- Oral GS-6207 + DVY (52 participants): headache (13.5%, 7 participants), nausea and lymphadenopathy (each 11.5%, 6 participants) and COVID-19, syphilis, diarrhea, and influenza (each 9.6%, 5 participants)

- BVY (25 participants): syphilis and arthralgia (each 16.0%, 4 participants) and headache, COVID-19, back pain, weight increased, upper respiratory tract infection, and insomnia (each 12.0%, 3 participants)

The majority of the AEs reported in the 4 treatment groups were Grade 1 or 2 in severity. The percentage of participants with AEs of Grade 3 or higher was 8.3% (13 of 157 participants) in the GS-6207 total group and 8.0% (2 of 25 participants) in the BVY group. No AEs of Grade 3 or higher were reported for > 1 participant in any treatment group.

Since the Week 28 analysis, 2 additional AEs of Grade 3 or higher were reported in the GS-6207 total group (SC GS-6207 + [DVY → TAF] group: 1 participant; SC GS-6207 + [DVY → BIC] group: 1 participant]) and 1 additional AE of Grade 3 or higher was reported in the BVY group (1 participant).

The percentages of participants with treatment-related AEs were as follows:

- GS-6207 total (157 participants): 43.9% (69 participants)

- SC GS-6207 total (105 participants): 58.1% (61 participants)

- Oral GS-6207 + DVY (52 participants): 15.4% (8 participants)

- BVY (25 participants): 16.0% (4 participants)

The higher frequency of treatment-related AEs in the SC GS-6207 total group was mainly because of ISRs, as reflected in the most common AEs considered related to study drugs:

- GS-6207 total group (157 participants), excluding ISRs: nausea (5.1%, 8 participants), diarrhea and headache (each 2.5%, 4 participants), and fatigue (1.9%, 3 participants)

- SC GS-6207 total group (105 participants), only ISRs: injection site erythema (26.7%, 28 participants), injection site swelling (22.9%, 24 participants), injection site pain (19.0%, 20 participants)

- Oral GS-6207 + DVY (52 participants): nausea and diarrhea (each 3.8%, 2 participants), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, influenza, overdose, and hot flush (each 1.9%, 1 participant)

- BVY (25 participants): dyspepsia, salivary hypersecretion, insomnia, and weight increased (4.0%, 1 participant)

Overall, 57 of 103 participants (55.3%) who received SC GS-6207 had a study drug-related ISR; all were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule. There were no new Grade 3 or higher ISRs reported since the Week 28 analysis. The most frequently reported ISRs (≥ 10% in SC GS-6207 total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site erythema (27.2%, 28 participants), 5 (2, 11) days
- Injection site swelling (23.3%, 24 participants), 11 (6, 29) days
- Injection site pain (19.4%, 20 participants), 4 (1, 9) days
- Injection site nodule (14.6%, 15 participants), 195 (122, 301) days
- Injection site inflammation (13.6%, 14 participants), 3 (1, 8) days
- Injection site induration (12.6%, 13 participants), 202 (101, 361) days

Overall, 15 of 103 participants had an AE of injection site nodule and 13 of 103 participants had an AE of injection site induration. All were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule. Ongoing and resolved injection site indurations and nodules were as follows:

ISRs after the first SC GS-6207 injection at Day 15:

Participant-level analysis:

- Nodules: Ongoing (1 of 11 [9.1%]); Resolved (10 of 11 [90.9%])
- Indurations: Ongoing (6 of 9 [66.7%]); Resolved (3 of 9 [33.3%])

Event-level analysis:

- Nodules: Ongoing (1 of 13 [7.7%]); Resolved (12 of 13 [92.3%])
- Indurations: Ongoing (6 of 9 [66.7%]); Resolved (3 of 9 [33.3%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 278 (136, 366) days and 202 (101, 213) days, respectively.

ISRs after the second SC GS-6207 injection at Week 28:

Participant-level analysis:

- Nodules: Ongoing (5 of 8 [62.5%]); Resolved (3 of 8 [37.5%])
- Indurations: Ongoing (3 of 6 [50.0%]); Resolved (3 of 6 [50.0%])

Event-level analysis:

- Nodules: Ongoing (5 of 8 [62.5%]); Resolved (3 of 8 [37.5%])
- Indurations: Ongoing (3 of 6 [50.0%]); Resolved (3 of 6 [50.0%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 152 (123, 240) days and 145 (4, 258) days, respectively.

CONCLUSIONS:

The conclusions from the Week 54 interim analysis of Study GS-US-200-4334 are as follows:

- High rates of virologic suppression continued to be maintained through Week 54. For the primary efficacy end point, overall, 136 of 157 participants (86.6%) who received SC or oral GS-6207 and 23 of 25 participants (92.0%) who received BVY had HIV-1 RNA < 50 copies/mL at Week 54.
- For participants with HIV-1 RNA < 50 copies/mL at Week 28, high rates of virologic suppression continued to be maintained through Week 54.
- Subcutaneously and orally administered GS-6207 remained generally safe and well tolerated.

1.3. Information About Bictegravir

Bictegravir (BIC, B) is a potent integrase strand transfer inhibitor (INSTI) that has been evaluated for the treatment of HIV-1 infection and that has demonstrated a terminal half-life suitable for once daily administration without a boosting agent.

1.3.1. General Information

For further information on BIC, please refer to the IB. Information in the IB includes:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.4. Information About Tenofovir Alafenamide

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that as its intracellular active moiety, tenofovir diphosphate (TFV-DP), inhibits HIV-1 reverse transcription. Tenofovir alafenamide (TAF) is an oral phosphonamidate prodrug of TFV. Tenofovir alafenamide is more stable in plasma than tenofovir disoproxil fumarate (TDF), provides higher intracellular levels of the active phosphorylated metabolite TFV-DP to target cells.

1.4.1. General Information

For further information on TAF, please refer to the IB. Information in the IB includes:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.5. Information About Emtricitabine/Tenofovir Alafenamide

Tenofovir is a nucleotide analog with limited oral bioavailability that as its intracellular active moiety, TFV-DP, inhibits HIV-1 reverse transcription. Tenofovir alafenamide is an oral phosphonamidate prodrug of TFV. Tenofovir alafenamide is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite TFV-DP to target cells. TAF in combination with emtricitabine (FTC) (F/TAF) forms an N(t)RTI backbone that can be combined with different third agents for the treatment of PLWH.

In 2016, US and international guidelines for the treatment of HIV infection were updated to include F/TAF as part of several recommended regimens for initial treatment of ART-naive, PLWH {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016, Saag 2018}. In both current guidelines ({Department of Health and Human Services (DHHS) 2011, European AIDS Clinical Society (EACS) 2018}), F/TAF is recommended for initial therapy in most PLWH in combination with an INSTI, specifically dolutegravir or BIC (available as BIKTARVY® [BVY, B/F/TAF]), or raltegravir (RAL).

1.5.1. General Information

For further information on F/TAF, please refer to the IB. Information in the IB includes:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.6. Information About Bictegravir/Emtricitabine/Tenofovir Alafenamide

Bictegravir/F/TAF is a fixed-dose combination (FDC) tablet for the treatment for HIV-1 infection. The B/F/TAF FDC tablet is a safe and highly effective INSTI-based treatment regimen, offering minimal pill burden, once-daily dosing, and excellent tolerability. The B/F/TAF FDC is a recommended initial treatment for PLWH {Department of Health and Human Services (DHHS) 2013}.

1.6.1. General Information

For further information on B/F/TAF, please refer to the IB. Information in the IB includes:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.7. Rationale for This Study

Advances in ART have led to significant improvements in morbidity and mortality among people living with HIV by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. While combination ARV therapy for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality associated with HIV disease, there remains a significant medical need for new well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, and new options for regimen simplification.

The goal of this study is to systematically evaluate potential combination regimens containing the novel capsid inhibitor, GS-6207, in treatment-naïve PLWH as an induction regimen and in virologically-suppressed people as a maintenance regimen. Participants who do not meet criteria for viral suppression will not be permitted to initiate a maintenance regimen using fewer agents than the induction regimen. The data are intended to support the ongoing clinical development of SC and oral GS-6207 for PLWH. The regimen of oral GS-6207+F/TAF will provide a positive control for the dual agent maintenance groups as well as support this combination for further development. An active control group of B/F/TAF is included as a current standard-of-care comparator.

1.8. Rationale for Dose Selection

1.8.1. GS-6207

The dose selection for GS-6207 in this study is supported by antiviral activity, PK, and safety data from the ongoing Phase 1b POC (study GS-US-200-4072) in treatment-naive and treatment experienced but CAI-naïve PLWH, as well as PK and safety data from the two Phase 1 studies in healthy volunteers (Studies GS-US-200-4538 and GS-US-200-4071).

In the ongoing Phase 1b POC study (GS-US-200-4072), potent antiviral activity of GS-6207 has been demonstrated; the mean maximum HIV-1 RNA decline over 10-day monotherapy after single SC doses of 50 mg to 450 mg was 1.8 to 2.2 log_{10} copies/mL, respectively. All participants achieved at least 1 log_{10} copies/mL decline in their HIV-1 RNA at Day 10. Day 10 antiviral activity was comparable across a single dose range of 50 mg to 450 mg. At these doses, mean (% CV) GS-6207 concentrations on Day 10 were 1.1- to 9.9-fold higher (ie, IQ 1.1 to 9.9) than the protein adjusted (pa)EC_{95} for wild type HIV-1 ($paEC_{95}$ = 3.87 ng/mL in MT-4 cells) (see Section 1.2.2.2).

Based on these data and the safety data available to date, a concentration target of at least 15.5 ng/mL for C_{trough} (corresponding to IQ4 based on $paEC_{95}$ from MT-4 cells) has been selected to ensure adequate antiviral activity would be achieved throughout dosing. GS-6207 formulations and doses to be evaluated in this study are informed by PK and safety data from Phase 1 studies, GS-US-200-4071 and GS-US-200-4538, in healthy volunteers.

In Treatment Groups 1, 2 and 3, the proposed GS-6207 regimens target an exposure whereby the lower bound of the 90% CI of the C_{trough} is at least 4-fold higher than the $paEC_{95}$ (ie, IQ4; 15.5 ng/mL) starting within a few days of dosing initiation and maintained throughout the dosing interval.

In Treatment Groups 1 and 2, participants will receive a SC GS-6207 regimen (every 26 weeks), preceded by an oral PK loading regimen. As described in Section 1.2.2.5, GS-6207 SC Injection (309 mg/mL) exhibits a slow initial release necessitating oral PK loading prior to the first SC injection to achieve IQ4 within a few days of initiation of dosing, participants will receive oral tablet doses of GS-6207 600 mg on Days 1 and 2, and 300 mg on Day 8. Participants will then receive GS-6207 927 mg SC on Day 15, followed by GS-6207 927 mg SC administered every 6 months (every 26 weeks). This regimen is projected to achieve target exposures within a few days of initiation, and to maintain throughout the 26 weeks SC dosing interval.

In Treatment Group 3, participants will receive an oral daily regimen of GS-6207. Participants will receive oral tablet doses of GS-6207 600 mg on Days 1 and 2, as a PK load, and 50 mg once daily, starting from Day 3. This regimen is projected to achieve target exposures within a few days of initiation. Based on available PK data (GS-US-200-4071), GS-6207 50 mg once daily is predicted to achieve a similar C_{max} as GS-6207 927 mg SC, administered every 26 weeks in Treatment Groups 1 and 2.

Safety data from studies GS-US-200-4071 and GS-US-200-4538 demonstrated favorable safety and tolerability profile of GS-6207 administered as single oral doses of up to 1800 mg, multiple oral daily doses of up to 100 mg or single SC doses of up to 927 mg. GS-6207 exposures in this study are predicted to be within the range of those shown to be safe and well tolerated; thereby, supporting further evaluation of this regimen in this study.

1.8.2. F/TAF and TAF

In Cohorts 1, 2 and 3, participants will receive F/TAF once daily (during the induction phase for Cohorts 1 and 2, and throughout Cohort 3), and in Cohort 1, participants will receive oral once daily TAF 25 mg during the maintenance period in combination with SC GS-6207. Both the F/TAF FDC containing F (200 mg) and TAF (25 mg), and TAF 25 mg single agent have been approved by the US Food and Drug Administration (FDA) as a component of several regimens, for use once daily for the treatment of HIV-1 infection in adults, or for treatment of hepatitis B virus (HBV) {BIKTARVY 2019, DESCOVY® 2017, VEMLIDY® 2019}.

1.8.3. BIC

In the maintenance period of Cohort 2, participants will receive oral once daily BIC (75 mg) in combination with SC GS-6207. The PK of BIC 75 mg has been evaluated previously at this dose: BIC exposure is similar to that observed in the B/F/TAF Phase 2/3 clinical program, where it was shown to be safe and well tolerated {BIKTARVY 2019}.

1.8.4. B/F/TAF

In Cohort 4, participants will receive B/F/TAF. The B/F/TAF FDC containing B (50 mg), F (200 mg), and TAF (25 mg), has been approved by the US-FDA for use once daily for the treatment of HIV-1 infection in adults {BIKTARVY 2019}.

1.9. Rationale for Oral Weekly Bridging of GS-6207 for Missed SC Injection

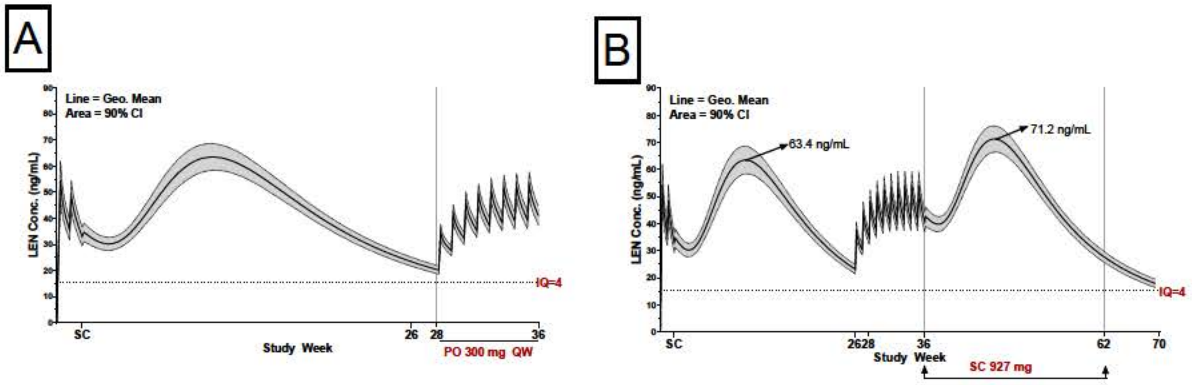
Participants receiving SC GS-6207 may miss their SC injection window (within 26 to 28 weeks of the previous SC GS-6207 dose [Section 5.3]). If a missed dose is anticipated, participants may receive oral bridging until they can receive their next SC injection.

Oral bridging of GS-6207 is supported by antiviral activity, PK, and safety data from a Phase 1b proof of concept study (GS-US-200-4072) and 2 ongoing Phase 2 and 2/3 studies (GS-US-200-4334 and GS-US-200-4625), as well as PK and safety data from 2 Phase 1 studies in healthy volunteers (GS-US-200-4071 and GS-US-200-4333). Phenotypic analyses and PK/PD modeling indicate that a GS-6207 plasma concentration of 15.5 ng/mL, corresponding to IQ of 4 or higher, would provide near maximal antiviral activity (GS-US-200-4072).

The oral bridging dose of GS-6207 is 300 mg administered once weekly starting 26 to 28 weeks after the last GS-6207 SC injection. This oral weekly bridging dose, even when started as late as 28 weeks after the last GS-6207 SC injection, is predicted to immediately maintain the lower bound of the 90% CI of arithmetic mean for GS-6207 C_{tau} above IQ4 (ie, even before reaching steady state) (Figure 1-9A). As long as the oral weekly bridging is initiated between 26 to 28 weeks after the last GS-6207 SC injection, the PK profile upon resuming SC injection is predicted to be comparable with that of the prior SC dose and within the target range regardless of when SC injection is resumed (Figure 1-9B).

GS-6207 has been administered orally at doses up to 1800 mg (Study GS-US-200-4071). Safety data from all completed and ongoing clinical studies indicate that GS-6207 is generally safe and well tolerated at the intended exposures.

Figure 1-9. Simulated Pharmacokinetic Profile of Oral Weekly Bridging of GS-6207 (300 mg) (A) Prior to and (B) After Resuming SC Injection



CI = confidence interval; IQ = inhibitory quotient; LEN = lenacapavir (GS-6207); PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; SC = subcutaneous; QW = once weekly
The solid line and the shaded region correspond to the geometric mean and 90% CI, respectively. IQ is calculated as trough concentration/in vitro protein-adjusted EC95 (paEC95) against wild-type virus. Horizontal dashed lines correspond to target IQ values of 4 based on phenotypic analyses and PK/PD modeling.

1.10. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown 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 PLWH include prolonged exposure to sub therapeutic concentrations of GS-6207 if it is discontinued which could lead to HIV-1 developing resistance to GS-6207. Strategies to mitigate any potential risks include use of a regimen with at least three ARVs during the induction phase and with at least two ARVs during the maintenance phase. In addition, all participants will have regular monitoring of their HIV-1 level to allow early selection of alternative therapies in the event of inadequate response. Participants will be advised to initiate alternative therapy for HIV if they discontinue from the study.

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

During the period of a pandemic (such as COVID-19), additional potential risks to participants may include interruptions to study visit schedule, inadequate study drug availability, and unrecognized safety issues due to interruptions in adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 5 for further details on the risks and risk mitigation strategy.

1.11. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of GS-6207 (Lenacapavir, LEN) containing regimens in people living with HIV (PLWH) as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54

The secondary objectives of this study are:

- To evaluate the efficacy of GS-6207 containing regimens in PLWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80
- To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80
- To evaluate the safety and tolerability of GS-6207 containing regimens through 28, 38, 54, and 80 weeks of treatment
- To evaluate the PK of GS-6207, BIC, and TAF

CCI

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the FDA-defined snapshot algorithm

The secondary endpoints of this study are:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the FDA-defined snapshot algorithm
- The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80

3.2. Study Design

This is a Phase 2, randomized, open label, active controlled, multicenter study.

Treatment-naïve PLWH who meet all eligibility criteria will be randomized in a 2:2:2:1 ratio to 1 of the 4 treatment groups. Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

3.3. Study Treatments

Approximately 175 participants who meet all eligibility criteria may be enrolled in this study in one of the following treatment groups:

Treatment Group 1

Induction: Participants will receive oral GS-6207 600 mg, 600 mg, and 300 mg, without regard to food, at Days 1, 2, and 8 respectively. Participants will also begin oral daily F/TAF (200/25 mg), without regard to food from Day 1 onwards for a total of 28 weeks. On Day 15 participants will receive SC GS-6207 927 mg, without regard to food.

Maintenance: Participants will receive SC GS-6207 927 mg at Week 28 and every 26 weeks thereafter. Participants will discontinue oral daily F/TAF (200/25 mg) at Week 28 and begin taking oral daily TAF (25 mg), without regard to food.

Treatment Group 2

Induction: Participants will receive oral GS-6207 600 mg, 600 mg, and 300 mg, without regard to food at Days 1, 2, and 8 respectively. Participants will also begin oral daily F/TAF (200/25 mg), without regard to food from Day 1 onward for a total of 28 weeks. On Day 15 participants will receive SC GS-6207 927 mg, without regard to food.

Maintenance: Participants will receive SC GS-6207 927 mg at Week 28 and every 26 weeks thereafter. Participants will discontinue oral daily F/TAF (200/25 mg) at Week 28 and begin oral daily BIC (75 mg) without regard to food.

Treatment Group 3

Participants will receive oral GS-6207 600 mg, and 600 mg without regard to food at Days 1 and 2, respectively. On Day 3, participants will begin oral daily GS-6207 50 mg, without regards to food. Participants will begin oral daily F/TAF (200/25 mg), without regard to food from Day 1 onwards.

Treatment Group 4

Participants will receive oral daily B/F/TAF (50/200/25 mg), without regard to food at Day 1 and throughout their participation in the study.

Randomization will be stratified as defined in Section 5.1.

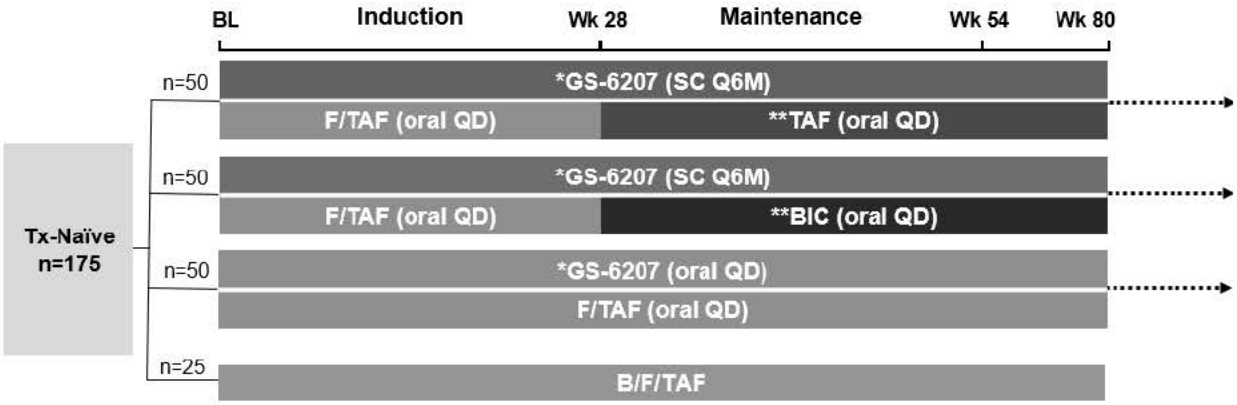
3.4. Duration of Treatment

Participants will be treated for at least 80 weeks. Participants in Treatment Group 4 will complete the study at Week 80.

At Week 80, participants receiving GS-6207 will be given the option to receive further treatment and continue to attend visits on Week 90, Week 106, Week 116, Week 132, Week 142, and will continue to alternate between every 10 weeks and every 16 weeks visits. Participants willing to continue the study beyond Week 80 in Treatment Groups 1 and 2 will continue to receive SC GS-6207 927 mg every 6 months (26 weeks) from Week 80 onwards and participants in Treatment Group 3 will continue to receive oral GS-6207 50 mg (daily) from Week 80 until product becomes accessible to participants through an access program, or until Gilead elects to discontinue the study in the country. Participants in Treatment Groups 1, 2, and 3 will also receive TAF, F/TAF, or BIC as applicable.

Participants who discontinue study drugs prior to Week 80 visit or prior to study completion may be required to complete 30-Day, 90 Day and/or 180-Day Follow Up visits after Early Termination Visit as described in Section 6.4.2.

Figure 3-1. Study Schema



*Treatment Groups 1, 2 and 3 will have oral PK loading doses
**Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study at Week 28.

BIC, B = bictegravir; BL = baseline; F = emtricitabine; HIV-1 = human immunodeficiency virus type 1; PK = pharmacokinetic; QD = once daily; Q6M = every 6 months; SC = subcutaneous; TAF = tenofovir alafenamide; Tx-naïve = treatment naïve; Wk = week.

[redacted]

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 175 PLWH who meet the eligibility criteria will be enrolled in one of 4 treatment groups.

4.1.1. Participant Replacement

Participants who discontinue prior to the end of study will not be replaced.

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent prior to performing study procedures
2) Aged ≥ 18 years
3) Antiretroviral naïve with no use of any ARV within one month of Screening. Use of pre-exposure prophylaxis (PrEP) (any duration), post-exposure prophylaxis (PEP) (any duration), or HIV-1 treatment (< 10 days therapy total) > 1 month prior to Screening is permitted
4) Plasma HIV-1 RNA ≥ 200 copies/mL at Screening
5) CD4+ cell count ≥ 200 cells/μL at Screening
6) A negative serum pregnancy test is required for all women at screening
7) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as defined in Appendix 4.
8) Lactating women must agree to discontinue nursing before the study drug(s) is administered

4.3. Exclusion Criteria

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

1) An opportunistic illness requiring acute therapy within 30 days prior to screening
2) Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days before screening
3) Active tuberculosis infection
4) Acute hepatitis within 30 days prior to screening

5) HBV infection, defined as screening results showing either or both of:

   a) Positive HBV surface antigen

   b) Positive HBV core antibody and negative HBV surface antibody

6) Hepatitis C virus (HCV) antibody positive and HCV RNA > lower limit of quantitation (LLOQ)

7) A history of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding)

8) Treatment within 3 months prior to screening, or anticipated treatment during the study period with immunosuppressant therapies, hydroxyurea, foscarnet, radiation, or cytotoxic chemotherapeutic agents without prior approval from sponsor prior to randomization. Agents disallowed in Table 5-5 may not be considered for approval

9) Active malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)

10) Current alcohol or substance use judged by the investigator to potentially interfere with the participant's study compliance

11) Clinically significant abnormal ECG at the screening visit

12) Any of the following laboratory values at screening

   a) Estimated glomerular filtration rate (eGFR) ≤ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}

   b) Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)

   c) Direct bilirubin > 1.5 × ULN

   d) Platelets < 50,000/mm^3

   e) Hemoglobin < 8.0 g/dL

13) Participation or planned participation in any other clinical trial (including observational trials) without prior approval from the sponsor throughout the study

14) Prior use of, or exposure to, GS-6207

15) Known hypersensitivity to the study drug(s), the metabolites, or formulation excipient

16) Use or planned use of exclusionary medications, refer to Section 5.4

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Participants will be assigned a screening number using the Interactive Web Response System (IWRS) on the day of the screening visit. **Randomization and Day 1 visits must not occur until participant eligibility has been confirmed.**

Once eligibility has been confirmed and prior to or during the Day 1 visit, the investigator or designee will randomize the participant using IWRS. Once a participant number has been assigned to a participant, it will not be reassigned to any other participant.

Randomization or enrollment may occur approximately 3 days prior to Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.

Participants who meet eligibility criteria will be randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups starting on Day 1. Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Lenacapavir (GS-6207) Injection, Lenacapavir (GS-6207) Tablets, TAF, F/TAF, B/F/TAF, and Bictegravir

5.2.1. Formulation

GS-6207 injection, 309 mg/mL, is a clear, yellow to brown solution for SC injection. In addition to the active ingredient (GS-6207 sodium salt), GS-6207 injection, 309 mg/mL, contains the following inactive ingredients: polyethylene glycol 300 and water for injection.

GS-6207 tablets, 300 mg are capsule-shaped, film-coated, beige tablets, debossed with “GSI” on one side of the tablet and “62L” on the other side of the tablet. Each tablet core contains the equivalent of 300 mg GS-6207 free acid in the form of GS-6207 sodium salt. In addition to the active ingredient, GS-6207 tablets 300 mg contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow.

GS-6207 tablets, 50 mg are capsule-shaped, film-coated green tablets, debossed with “GSI” on one side of the tablet and “07S” on the other side of the tablet. Each tablet core contains the equivalent of 50 mg GS-6207 free acid in the form of GS-6207 sodium salt. In addition to the active ingredient, GS-6207 tablets 50 mg contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide black, and iron oxide yellow.

TAF tablets, 25 mg are round, biconvex, film-coated yellow tablets, debossed with "GSI" on one side of the tablet and "25" on the other side of the tablet. Each tablet core contains 25 mg of TAF. In addition to the active ingredient, TAF 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.

F/TAF (200/25 mg) tablets are rectangular-shaped, film-coated blue tablets, debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. Each tablet core contains 200 mg of FTC and 25 mg of TAF. In addition to the active ingredients, F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

B/F/TAF (50/200/25 mg) tablets are capsule-shaped, film-coated, purplish-brown tablets, 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 BIC, 200 mg of FTC, and 25 mg of TAF. In addition to the active ingredients, 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.

Bictegravir tablets, 75 mg are yellow, round, plain-faced, film-coated tablets. In addition to BIC, each tablet contains lactose monohydrate, microcrystalline cellulose, crospovidone, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide yellow.

5.2.2. Packaging and Labeling

GS-6207 injection, 309 mg/mL, is supplied as a sterile solution packaged in a single use, clear vial fitted with a rubber stopper and an aluminum flip-off seal.

GS-6207 tablets, 300 mg are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 4 or 5 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

GS-6207 tablets, 50 mg are packaged in white, 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 fitted with an induction-sealed and aluminum-faced liner.

TAF tablets, 25 mg are packaged in white, 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 fitted with an induction-sealed and aluminum-faced liner.

F/TAF tablets, 200/25 mg are packaged in white, 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 fitted with an induction-sealed and aluminum-faced liner.

B/F/TAF tablets, 50/200/25 mg are packaged in white, 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 fitted with an induction-sealed and aluminum-faced liner.

Bictegravir tablets, 75 mg are packaged in white, HDPE bottles with polyester coil in each bottle. Each bottle contains 30 tablets and polyester packing material, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US-FDA and/or other local regulations.

5.2.3. Storage and Handling

GS-6207 injection, 309 mg/mL should be stored below 30°C (86°F), protected from light. Storage conditions are specified on the label.

GS-6207, 300 mg tablets should be stored below 30°C (86°F). Storage conditions are specified on the label.

GS-6207, 50 mg tablets should be stored below 30°C (86°F). Storage conditions are specified on the label.

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.

F/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.

B/F/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.

Bictegravir, 75 mg 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 participants, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of Study Drugs

All study drugs (Oral GS-6207, GS-6207 injection for SC administration, TAF, F/TAF, BIC, B/F/TAF) will be provided by Gilead.

Treatment Group 1 and 2 participants will be administered oral GS-6207 on Days 1, 2, and 8. GS-6207 will be administered without regards to food. The oral GS-6207 (300 mg) bottle will remain at investigator site and will not be given to the participants. Oral and SC dosing is presented in Table 5-1.

Table 5-1. GS-6207 Dosing for Treatment Group 1 and 2

Study Visits	GS-6207
Day 1	600 mg oral
Day 2	600 mg oral
Day 8	300 mg oral
Day 15	927 mg SC
Week 28 and every 26 weeks thereafter	927 mg SC

GS-6207 927 mg injection will be administered in the abdomen via SC injections on Day 15, Week 28, and every 6 months (26 weeks) thereafter. GS-6207 should be administered as multiple injections at different abdominal sites no more than 15 minutes apart when possible.

In addition to GS-6207, Treatment Group 1 and 2 participants will take oral daily F/TAF from Day 1 onwards approximately at the same time. F/TAF will be administered on-site on Day 1. The F/TAF bottle(s) can be kept on-site for Day 2 administration and should be given to participants at the end of Day 2 visit to take at home from Day 3 onwards. Treatment Group 1 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 will stop F/TAF at Week 28 and will initiate oral daily TAF. Treatment Group 2 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 will stop F/TAF at Week 28 and will initiate oral daily BIC.

Oral dosing on Day 1, Day 2, and Day 8 and all SC GS-6207 administrations will occur on site and without regard to food (for Oral Bridging Period, see 5.4).

If participants in Treatment Groups 1 and 2 are not dosed within the protocol visit windows, and the investigator believes that it is in the participant's medical interest to continue to receive GS-6207, Gilead should be contacted immediately, and the participant may continue to receive GS-6207 with the approval of the Gilead medical monitor. Additional oral GS-6207 doses may be needed prior to subsequent SC dosing (Section 5.4).

Table 5-2. GS-6207 Dosing for Treatment Group 3

Study Visits	GS-6207
Day 1	600 mg oral
Day 2	600 mg oral
Day 3 onwards	50 mg oral daily

Participants in Treatment Group 3 will be administered oral GS-6207, 600 mg, on Days 1 and 2. GS-6207 will be administered without regards to food. The oral GS-6207 (300 mg) bottle will remain at the investigator site and will not be given to the participants.

In addition to oral GS-6207, participants in Treatment Group 3 will take oral F/TAF daily from Day 1 onwards approximately at the same time. Dosing of GS-6207 and F/TAF will occur on-site on Day 1. The GS-6207 50 mg bottle(s) and F/TAF bottle(s) can be kept on-site and should be given to the participants by end of Day 2 visit. Participants will take 50 mg of GS-6207 oral daily and F/TAF oral daily together at approximately the same time from Day 3 onwards. Oral GS-6207 dosing is presented in Table 5-2.

Treatment Group 4 participants will take B/F/TAF orally daily at approximately the same time. Administration of dose on Day 1 will occur on-site and without regard to food.

For participants in all treatment groups, the date and time of the last meal prior to dosing will be collected.

5.4. Dosing and Administration of Oral Weekly Bridging of GS-6207

Participants in Treatment Groups 1 and 2 may require oral weekly bridging if an SC injection of GS-6207 cannot be administered for any reason within the protocol visit window.

- If 26 to 28 weeks elapses since the last SC injection and if clinically appropriate to continue GS-6207, start oral GS-6207 300 mg (1 tablet) once a week at Oral Bridging visits and continue weekly dosing on the same day of the week.

- If more than 28 weeks elapse since the last SC injection and if clinically appropriate to continue GS-6207, restart the oral lead-in at the Oral Bridging visits and continue oral weekly dosing on the same day of the week, until SC GS-6207 is administered (**Table 5-3**).

Table 5-3. Dosing Schedule for Oral Weekly Bridging and Resumption of SC GS-6207 Injection

26 to 28 weeks of elapse since the last SC injection	More than 28 weeks of elapse since the last SC injection	GS-6207 Dose
Treatment time from oral start	**Dose**	
N/A	Day 1[a]	Oral 600 mg (2 x 300 mg tablets)
N/A	Day 2	Oral 600 mg (2 x 300 mg tablets)
Day 1[a]	Day 8; continue oral weekly GS-6207 on the same day of the week as first dose until GS-6207 SC is administered	Oral 300 mg (1 x 300 mg tablet)
Day 8; continue oral weekly GS-6207 on the same day of the week as first dose until GS-6207 SC is administered	Not applicable	Oral 300 mg (1 x 300 mg tablet) once a week
SC administration restart (within one week of the oral weekly 300 mg dose [as early as after Day 1 dosing])	SC administration restart (within one week of the oral weekly 300 mg dose [as early as after Day 8 dosing])	SC 927 mg every 6 months[a]

N/A = not applicable; SC = subcutaneous
a Day 1 oral dosing and SC GS-6207 will be administered on site, otherwise, all other oral dosing will be administered at home, but can be done on site at the investigator's discretion.

- For oral weekly bridging, the administration of the first dose will occur on-site and up to 2 bottles of GS-6207 will be given to the participant to take oral GS-6207 at home; further on-site oral dosing may occur at investigator's discretion. Up to 2 additional bottles may be given to the participant as needed upon completion of previously dispensed bottles.

- Participants may continue receiving oral weekly GS-6207 300 mg until they can receive their next SC GS-6207 injection.

- If oral weekly GS-6207 administration is expected to be needed beyond 12 consecutive weeks, Gilead should be contacted and further additional oral weekly doses can be provided after assessment unless other guidance is provided by Gilead.

- Monitoring of participants should continue according to the study protocol. Oral Bridging visit should be completed every 10-12 weeks. Additional visits during the oral weekly administration may be conducted per investigator's discretion

- Missed dose recommendations for oral weekly bridging are provided in **Table 5-4**. The scheduled dosing day of the week should not change due to the missed dose of GS-6207.

Table 5-4. Missed Dose Recommendations for GS-6207 During Oral Weekly Bridging

Number of days since initial missed schedule dose	Recommendation	Example
1 to 6 days (1 missed dose)	Take 1 dose as soon as possible, then resume normal schedule, taking 1 dose on the next scheduled day	Participant forgets to take dose on Monday (scheduled) but remembers before the next scheduled dose day (ie, Tuesday-Sunday). Take 1 dose as soon as possible, then take 1 dose on the following Monday as scheduled.
7 to 14 days (1 - 2 missed doses)	Take 2 doses as soon as possible, then resume normal schedule on scheduled day. If participant remembers on scheduled dosing day, then take 2 doses only. Never take 3 doses on the same day.	Participant forgets to take dose on Monday (scheduled) but remembers the following Monday. Take 2 doses on the second Monday and resume dosing schedule (1 dose on Mondays). Participant forgets to take dose on 2 consecutive Mondays (scheduled) but remembers a few days later (ie, Tuesday-Sunday following second missed dose) before the third Monday. Take 2 doses as soon as possible, then take 1 dose the next Monday as scheduled. Participant forgets to take dose on 2 consecutive Mondays (scheduled) but remembers on the third Monday. Take 2 doses on the third Monday and resume dosing schedule (1 dose on Mondays). Never take 3 doses on the same day.
More than 14 days (3 or more missed doses)	Assess whether clinically appropriate to continue oral weekly bridging. Consider checking HIV-1 RNA.	Participant forgets to take dose on 3 consecutive Mondays (scheduled). Clinical assessment needed.

5.5. Prior and Concomitant Medications

Clinical data indicate GS-6207 is a substrate of P-gp transporters and an inhibitor of CYP3A (moderate), BCRP and P-gp. In vitro data suggest GS-6207 is also a substrate of CYP3A and UGT1A1 enzymes. Concomitant use of GS-6207 with some medications or herbal/natural supplements that are inhibitors and inducers of CYP3A, UGT1A1 or P-gp may result in increased or decreased exposure of GS-6207 respectively.

Concomitant use of GS-6207 with some medications or herbal/natural supplements that are substrates of CYP3A, P-gp or BCRP may result in increased exposure of these medications.

Representative medications listed Table 5-3 and herbal/natural supplements are currently excluded or should be used with caution while participating in this study; this table is not exhaustive. For medications that may be substrates of Pgp, CYP3A, UGT1A1 or BCRP, or those that may be inducers, the investigator should reach out to Gilead for guidance.

Participants should discontinue disallowed concomitant medications 30 days prior to initiation of study drug, unless otherwise specified.

Table 5-5. List of Representative Medications that are Prohibited or To Be Used with Caution due to the Potential for Drug-Drug Interaction with GS-6207

Medication Class	Disallowed Medications	Use Discouraged and To Be Used With Caution
Anti-coagulants		Dabigatran etexilate: monitoring and/or dose reduction may be needed for certain populations per prescribing information
Anti-convulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	
Anti-mycobacterials	Rifampin, Rifabutin, Rifapentine	
Anti-retroviral agents	Any ARV not part of the study treatment regimen	
Digoxin		Digoxin: Concomitant use may result in increased levels of digoxin; use with caution and with appropriate monitoring of serum digoxin levels
Ergot derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine	
Herbal/Natural Supplements	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) Reductase Inhibitors		Concentrations of some statins may increase with GS-6207. Start with the lowest dose and titrate to clinical response. For each of the following statins, the maximum allowed dose is: Simvastatin: 10 mg Lovastatin: 20 mg Atorvastatin: 40 mg Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.
Phosphodiesterase-5 Inhibitors		Sildenafil, Vardenafil, Tadalafil: It is recommended that a single dose of Sildenafil no more than 25 mg in 48 hours, Vardenafil no more than 2.5 mg in 72 hours, or Tadalafil no more than 10 mg in 72 hours be coadministered.
Sedatives/Hypnotics		Midazolam, Triazolam

Medication Class	Disallowed Medications	Use Discouraged and To Be Used With Caution
Systemic Corticosteroids	All agents, including dexamethasone	

For participants in Treatment Groups 1, 2, and 3, physicians should also refer to the most current package insert for F/TAF for guidance on concomitant medications while participants are receiving treatments containing TAF (TAF single agent or F/TAF).

For participants in Treatment Groups 2 and 4, physicians should also refer to the most current package insert for B/F/TAF for guidance on concomitant medications while the participants are receiving BIC.

Medications to treat disease conditions excluded from the protocol are not listed under this Concomitant Medication section and are disallowed in the study. Medications for malignancy are not included in the table.

Should participants have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where disallowed medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as they are aware of the use of the medication.

5.6. Accountability for Investigational Medicinal Product

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

Each study site must keep accountability records that capture:

- the date received and quantity of study drug kits
- the date, participant number, and the study drug kit number dispensed
- the date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.6.1. Investigational Medicinal Product Return or Disposal of GS-6207, TAF, F/TAF, BIC, and B/F/TAF

Gilead recommends that used and unused study drug supplies be destroyed at the site. 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 electronic trail master file (eTMF). If study drug is destroyed on-site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

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

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

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit, unless otherwise agreed with the sponsor and documented.

6. STUDY PROCEDURES

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

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

6.1. Participant Enrollment and Treatment Assignment

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

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent
- Obtain demographic information, including gender at birth, sexual orientation, and gender identity
- Obtain medical history including HIV-1 disease-related events, available historical genotype/phenotype reports and prior medications within 30 days of the screening visit. Samples for genotype reports will be collected at screening but results are not required to determine eligibility.
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator) including, vital signs (blood pressure, pulse, respiration rate, and temperature, body weight, and height)
- 12-lead ECG performed supine
- Obtain blood and urine samples as noted in Section 6.5
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form.

Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for randomization into the study.

Participants not meeting one or more inclusion criteria and/or meeting one or more exclusion criteria may be rescreened on a case-by-case basis upon written approval from Gilead Medical Monitor or Study Director.

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

6.3. Treatment Assessments

6.3.1. Day 1

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization and the Day 1 visit. Participants must complete all study procedures before being administered study drug:

- Prior to the completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available)
  - HIV dependent quality of life (HIVDQoL) and EQ-ED-5L
- 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 (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.5
- Dispense study drug(s) based on participant's treatment assignment at randomization:
  - Participants randomized to Treatment Group 1, 2, and 3 will be dispensed PK loading doses of oral GS-6207 (600 mg) and F/TAF (200/25 mg). Bottle of 300 mg GS-6207 will remain at site for in-clinic observed dosing. Bottle of F/TAF can remain at site on Day 1 and Day 2 for in-clinic observed dosing and then will be given to participant at the end of Day 2 visit for subsequent daily dosing at home.
  - Participants randomized to Treatment Group 3 will be dispensed oral GS-6207 (50 mg). Participants may be given bottle of oral GS-6207 (50 mg) at the end of Day 2 visit to initiate dosing from Day 3 onwards only.
  - Participants randomized to Treatment Group 4 will be dispensed oral daily B/F/TAF (50/200/25 mg)

- Observed first dose administration of the assigned study drugs as described in Section 5.3
  - Participants randomized to Treatment Group 1, 2, and 3 will be administered PK loading doses of oral GS-6207 (600 mg) and F/TAF (200/25 mg)
  - Participant randomized to Treatment Group 4 will be administered oral daily B/F/TAF (50/200/25 mg)

6.3.2. Day 2, CCI Day 8, and Day 15

The following evaluations are to be completed at Day 2, CCI (± 1 day) CCI [redacted], Day 8, and Day 15 for participants only in Treatment Groups 1, 2, and 3. Participants in Treatment Group 4 will have visits starting at Week 4 after Day 1.

- Prior to the completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available)
  - HIV Treatment Satisfaction Questionnaire (HIVTSQ12) **(Day 15)**
- Review of AEs and changes in concomitant medications
- Complete physical examination (**Day 15**), (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed CCI [redacted]
- Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight CCI [redacted]
- Obtain blood and urine samples as described in Section 6.5
- Document dispensation and accountability for GS-6207 CCI [redacted]
- Observed dose administration of the assigned study drugs as described in Section 5.3 (Days 2, 8, and 15 for Treatment Groups 1 and 2 only)
  - Day 2: Participants randomized to Treatment Groups 1, 2, and 3 will be administered PK loading doses of oral GS-6207 (600 mg).
  - Day 8: Participants randomized to Treatment Groups 1 and 2 will be administered PK loading doses of oral GS-6207 (300 mg).
- Instruct participant to initiate dosing of GS-6207 50 mg from Day 3 onwards (Treatment Group 3 only)
- GS-6207 SC injection for Treatment Group 1 and 2 participants only **(Day 15)**
  - Provide Injection Site Reaction Assessment Worksheet and instruct the participants to measure and report injection site reactions following the administration of the SC injections

- After administration of SC GS-6207 and completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available) **(Day 15)**

  — Injection Acceptability Questionnaire and Numeric Pain Rating Scale for participants randomized to Treatment Groups 1 and 2 only

6.3.3. Treatment Assessments (Week 4 – Week 28)

The following evaluations are to be completed at Week 4 and every 6 weeks until Week 28, unless otherwise specified.

All study visits are to be completed within ± 2 days of the protocol-specified visit date (based on the Day 1 visit), unless otherwise specified.

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

- Prior to completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available) **(Week 4, Week 28)**

  — HIV Treatment Satisfaction Questionnaire status (HIVTSQ12s), HIVDQoL, and EQ-ED-5L

- Review of AEs and changes in concomitant medications
- Complete physical examination (**Week 28**) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination, as needed
- Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.5
- Document bottle dispensation for study drug(s) for all visits

  — Participants randomized to Treatment Groups 1 and 2 will be dispensed F/TAF (200/25 mg) (**Week 4, Week 10, Week 16, Week 22**)

  — Participants in Treatment Group 1 will discontinue F/TAF and will be dispensed TAF (25 mg) (**Week 28**)

  — Participants in Treatment Group 2 will discontinue F/TAF and will be dispensed BIC (75 mg) (**Week 28**)

  — Participants randomized to Treatment Group 3 will be dispensed GS-6207 (50 mg) and F/TAF (200/25 mg)

  — Participant randomized to Treatment Group 4 will be dispensed B/F/TAF (50/200/25 mg)

- Document accountability for study drug(s) for all visit
- GS-6207 SC injection for Treatment Group 1 and 2 participants only (**Week 28**)
  - Provide Injection Site Reaction Assessment Worksheet and instruct the participants to measure and report injection site reactions following the administration of the SC injections
- Participants who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Section 6.7
- Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; HIV-1 RNA results ≥ 50 copies/mL will be assessed for virologic rebound as described in Section 6.7.2. Participants with confirmed HIV-1 RNA values ≥ 50 copies/mL will discontinue the study drug at or prior to Week 28
- After administration of SC GS-6207 and completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available)
  - Injection Acceptability Questionnaire and Numeric Pain Rating Scale for participants randomized to Treatment Groups 1 and 2 only **(Week 28 only)**

6.3.4. Post Week 28 Assessments

The following evaluations are to be completed at Week 38, Week 54, Week 64, and Week 80. At Week 80, participants in Treatment Group 4 will complete the study. Participants in Treatment Groups 1, 2, and 3 will be given the option to receive further treatment and continue to attend visits on Week 90, Week 106, Week 116, Week 132, Week 142, and will continue to alternate between every 10 weeks and every 16 weeks.

Week 28 through Week 80 study visits are to be completed within ± 2 days of the protocol-specified visit date (based on the Day 1 visit). Following the completion of the Week 80 visit, visits are to be completed within ± 6 days of the protocol-specified visit date. Each SC GS-6207 dosing should occur within 26 and 28 weeks of the previous SC GS-6207 dosing (unless there is no intervening Oral Bridging Period).

Participants in Treatment Groups 1 and 2 may require Oral Bridging if an SC injection of GS-6207 cannot be administered within the protocol visit window. In case of oral bridging initiation, participants will receive oral GS-6207 as specified in Section 5.4 and complete Oral Bridging visits. An Oral Bridging visit should be completed every 10-12 weeks. Additional visits during the oral weekly administration may be conducted per investigator's discretion. Upon restarting GS-6207 SC injection, a SC dosing visit will restart (ie, Week 80, Week 106), with follow-up visits in between occurring as specified in this protocol.

- Prior to the completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available) (**Week 54**)
  - HIV Treatment Satisfaction Questionnaire change (HIVTSQ12c), HIVDQoL, and EQ-ED-5L
- Prior to the completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available) (**Week 80**)
  - HIVTSQ12s, HIVDQoL, and EQ-5D-5L
- Review of AEs and changes in concomitant medications
- Complete physical examination (**Weeks 54, 80)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination, as needed
- Vital signs (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Section 6.5
- Document dispensation and accountability for study drug(s) for all visits
  - Participants in Treatment Group 1 will be dispensed TAF (25 mg)
  - Participants in Treatment Group 2 will be dispensed BIC (75 mg)
  - Participants randomized to Treatment Group 3 will be dispensed oral daily GS-6207 (50 mg) and F/TAF (200/25 mg)
  - Participant randomized to Treatment Group 4 will be dispensed oral daily B/F/TAF (50/200/25 mg) (**Week 38, Week 54, Week 64**)
- GS-6207 SC injection for Treatment Group 1 and 2 participants only (**Week 54 and every 26 weeks thereafter**)

Provide Injection Site Reaction Assessment Worksheet and instruct the participants to measure and report injection site reactions following the administration of the SC injections

- For all participants on oral weekly bridging, the first dose of oral GS-6207 will be administered at the study center without regard to food and up to two bottles will be provided to the participant with instructions to take the remaining doses at home once a week (1 × 300 mg GS-6207) without regard to food on the same day of the week that the first dose was given.
- After administration of SC GS-6207 and completion of other study procedures, participants will read the questionnaires by themselves and provide answers directly onto the questionnaires (if available) (**Week 54, Week 80**)

— Injection Acceptability Questionnaire and Numeric Pain Rating Scale for participants randomized to Treatment Groups 1 and 2 only

- Document study drug administration
- Document study drug accountability
- Participants who meet the criteria for virologic failure will be managed according to the Management of Virologic Rebound Section 6.7

6.4. Post-treatment Assessments

6.4.1. Early Termination Visit Assessments

6.4.1.1. Early Termination Visit Assessments - Treatment Group 1 and 2

6.4.1.1.1. Early Termination visit after Day 1 and prior to Day 15

If a participant discontinues oral GS-6207 or decides not to initiate SC GS-6207 at Day 15, an Early Termination Visit should be performed within 72 hours of the decision to discontinue the study drug. Participants will be asked to continue to attend study visits until completion of the Day 15 visit. Participants will be required to complete 90-Day Follow up Visit. Refer to Section 6.4.2

6.4.1.1.2. Early Termination visit after Day 15 and prior to Week 80

If a participant decides to discontinue GS-6207 (SC and oral) prior to Week 80, an Early Termination Visit should be performed within 72 hours of decision to discontinue study drug.

The participant will be asked to continue attending the scheduled study visits through the Week 80 visit.

- If the participant decides to discontinue SC GS-6207 but continues to attend study visits through Week 80, no follow up visits are required.
- If the participant decides to discontinue SC GS-6207 and does not continue to attend study visits through Week 80, the 30-Day, 90-Day and 180-Day Follow Up Visits are required. Refer to Section 6.4.2. The 180-Day follow up may be conducted via a phone call per the investigator's discretion.
- If a participant discontinues oral GS-6207 during the Oral Bridging Period and does not continue to attend study visits through their next SC dosing visit, the participant will be required to complete the 90-Day Follow up-Visit (see Section 6.4.2).

6.4.1.1.3. Early Termination visit after Week 80

If a participant continues the study after completing the Week 80 visit, but discontinues GS-6207 (SC and oral) prior to study completion, an Early Termination Visit should be performed within 72 hours of decision to discontinue study drug.

- If the participant decides to discontinue SC GS-6207 but continues to attend the scheduled study visits through their next SC dosing visit, they will complete all assessments except SC dosing at the last visit and complete the study. No further follow up visits are required.

- If the participant decides to discontinue SC GS-6207 and does not continue to attend the scheduled study visits through their next SC dosing visit, the 30-Day, 90-Day and 180-Day Follow Up Visits are required. Refer to Section 6.4.2. The 180-Day Follow Up may be conducted via a phone call per the investigator's discretion.

- If a participant discontinues oral GS-6207 during the Oral Bridging Period and does not continue to attend study visits through their next SC dosing visit, the participant will be required to complete the 90-Day Follow up Visit (see Section 6.4.2).

6.4.1.2. Early Termination Visit Assessments - Treatment Group 3

If the participant discontinues their study regimen prior to Week 64 visit, the participant will be asked to return to the clinic within 72 hours of stopping study treatment for an Early Termination visit. The participant will be asked to continue to attend study visits through Week 80.

- If the participant agrees to continue to attend study visits through Week 80, no follow up visits are required.

- If the participant does not agree to continue to attend study visits through Week 80, the 30-Day and 90-Day Follow Up Visits are required. Refer to Section 6.4.2

If a participant discontinues the study drug between Week 64 and Week 80 OR after completing the Week 80 visit but prior to study completion, the Early Termination visit should be performed. The participant will complete the 30-Day and 90-Day follow-up visits after completion of the Early Termination visit.

6.4.1.3. Early Termination Visit Assessments - Treatment Group 4

If the participant discontinues their study regimen prior to Week 64 visit, the participant will be asked to return to the clinic within 72 hours of stopping study drug for an Early Termination visit. The participant will be asked to continue to attend study visits through Week 80.

- If the participant agrees to continue to attend study visits through Week 80, no follow up visits are required.

- If the participant does not agree to continue to attend study visits through Week 80, the 30-Day Follow Up Visit is required. Refer to Section 6.4.2

If a participant discontinues the study drug between Week 64 and Week 80, the Early Termination visit should be performed. The participant will complete the 30-Day Follow-Up visit after completion of the Early Termination visit.

If there are any abnormal laboratory results with a possible or probable causal relationship with the study drug, every attempt should be made to keep the participant 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 participant or investigator, the participant may be withdrawn from the study.

If there are any AEs, every attempt should be made to keep the participant in the study and should be followed up until the AE is resolved or stable. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period. If this is not possible or acceptable to the participant or investigator, the participant 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), including weight
- Obtain blood and urine samples as noted in Section 6.5
- Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer participant to an appropriate HIV treatment facility

6.4.2. 30-Day, 90-Day and 180-Day Follow-up Visits

The assessments below will be completed for participants who are required to complete the 30-Day, 90-Day and 180-Day Follow-up visits as noted in Section 6.4.1.

Follow-up visits will be scheduled based on the date of the Early Termination Visit. For the purpose of scheduling the follow-up visits, a ±6 day window may be used.

The following evaluations are to be completed at the follow-up visits:

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

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

- Obtain blood and urine samples as noted in Section 6.5

At the 30-Day, 90-Day or 180-Day Follow-Up Visit, as applicable, if there are any abnormal laboratory results indicating that there is a possible or probable causal relationship with the study drug(s), every attempt should be made to 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 participant or investigator, the participant may be withdrawn from the study.

If there are any AEs, every attempt should be made to keep the participant in the study and should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

6.5. 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.

6.5.1. Blood Samples

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

- Serum pregnancy test for all women (**Screening only**)

- Serum follicle-stimulating hormone (FSH) test (FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure) (**Screening only**)

- Chemistry profile: alkaline phosphatase, AST, ALT, gamma-glutamyltransferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid CCI

- Nonfasting lipid panel: total cholesterol, high-density lipoprotein (HDL), direct low-density lipoprotein (LDL), and triglycerides CCI

- Estimated GFR CCI according to:

  — Cockcroft-Gault formula for Creatinine clearance for participants ≥ 18 years of age

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

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

- Hematology profile: complete blood count (CBC) with differential and platelet count CCI
- CD4+ cell count CCI
- Plasma HIV-1 RNA CCI
- HIV-1 genotype and phenotype at Screening visit and any subsequent visit with virologic failure (described in Section 6.7)
- HBV serologies (HBV surface antigen, HBV core antibody, HBV surface antibody) (**Screening only**)
- HCV antibody serology (**Screening only**)
- [redacted]
- Plasma storage samples for additional safety and virology testing (HIV-1 genotype and phenotype) CCI

6.5.2. Pharmacokinetic Assessments:

For Treatment Groups 1 and 2:

Plasma PK sampling will occur relative to dosing of GS-6207 at the following time points for all participants:

- Days 1, 2, and 8:
  - — Predose (within 30 minutes of dosing)
  - — A single timed PK sample between 1 and 6 hours postdose
- [redacted]
- At Day 15 and at all visits with GS-6207 SC injections, including when GS-6207 SC injection is resumed after the Oral Bridging Visits, if applicable: A single predose PK sample will be collected
- Starting at Week 4 visit, at all visits without GS-6207 SC injections, including the Oral Bridging visits, if applicable: A single anytime PK sample will be collected

CCI [redacted]

For Treatment Group 3:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits

CCI [redacted]

For Treatment Group 4:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits.

6.5.3. Blood Storage Samples

Any residual blood and urine samples collected at all visits (except the screening and Early Termination Visits) will be frozen and stored. CCI [redacted] No human genetic testing will be performed using these samples without consent of study participants.

CCI [redacted]

6.5.4. 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

- Urine pregnancy test for women of childbearing potential (except at Screening CCI visits)

  — If the test is positive, confirmatory serum test should be performed and study drug dosing should be delayed until results obtained

  — For participants in Treatment Groups 1 and 2, a confirmatory negative urine pregnancy test prior to subcutaneous GS-6207 administration must be completed.

- Urine storage for possible additional clinical testing (except at Screening, CCI and 30-Day, 90-Day, and 180-Day Follow-up visits, as applicable).

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant 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 participant's best interest

- Lack of efficacy

- Participant request to discontinue for any reason

- Participant noncompliance

- Pregnancy during the study; refer to Appendix 4.

- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)

- Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study drug at or prior to Week 28. If data are missing at either Weeks 16 or 22 the participants discontinuation should be discussed with the medical monitor.

CCI [redacted]

CCI [redacted]

[redacted]

6.8. End of Study

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

6.9. Post Study Care

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

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered an investigational 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 an investigational product, whether or not considered related to the investigational product. AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.7). 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 AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

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

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

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 study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE 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 AE has an etiology other than the study procedure.

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale.

The DAIDS scale is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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

Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable electronic case report forms (eCRFs): all SAEs and AEs related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-defined follow-up period, must be reported on the eCRFs as instructed.

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-defined follow-up period, must be reported on the applicable eCRFs and submitted to Gilead Global Patient Safety (GLPS) (formerly known as Pharmacovigilance an Epidemiology (PVE)) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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 the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug(s), the investigator should promptly document and report the event to Gilead GLPS.

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

7.3.2.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS 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 GLPS:	Gilead GLPS Email: PPD or Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed on the applicable eCRFs according to instructions and within the timelines outlined 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 email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US-FDA Code of Federal Regulations, the European Union (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, which may be in the form of line-listings, 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 IB or relevant local label as applicable.

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

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

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

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. 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.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice. If repeat testing is not possible within 3 calendar days of receipt of results, it may be completed within 14 calendar days of receipt of results per the Investigator's discretion.

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug(s) at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

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

For a Grade 3 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to study drug(s), then study drug(s) should be withheld until the toxicity returns to ≤ Grade 2.

If a clinically significant laboratory abnormality or clinical event recurs to ≥ Grade 3 following re-challenge with study drug(s) and is considered to be related to study drug(s), then study drug(s) should be permanently discontinued, and the participant managed according to local practice, including switching to an effective alternative ARV regimen with consideration of the long duration of exposure of GS-6207 CCI [redacted]. Recurrence of laboratory abnormalities considered unrelated to study drug(s) may not require permanent discontinuation but requires discussion with the Gilead medical monitor.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to study drug(s), then study drug(s) should be permanently discontinued, and the participant managed according to local practice, including switching to an effective alternative ARV regimen with consideration of the long duration of exposure of GS-6207 CCI [redacted]. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

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

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided.

Whether or not considered treatment-related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

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

7.6.4. Management of Adverse Events of Injection Site Reactions of Grade 3 or Higher, or Persisting for More Than 26 Weeks

In clinical studies of SC GS-6207, Grade 3 or higher AEs of injections site reactions (ISRs) were uncommon. Some participants experienced AEs of injection site nodule and induration, which decreased in size over 6 months or longer. For AEs of ISRs related to SC GS-6207 administered from a borosilicate vial that are Grade 3 or higher or persisting for more than 26 weeks, particularly nodule and/or induration, the investigator must contact the medical monitor and obtain consultation with an independent dermatologist to evaluate the ISRs.

If clinically indicated as determined by the independent dermatologist, a biopsy of the SC injection site may be performed. The histopathology should be reviewed by an independent dermatopathologist; if a dermatopathologist is not locally available, the histopathology may be reviewed by an otherwise medically qualified person.

Photographic documentation of the ISRs that meets the criteria above is recommended, if possible, but is not mandatory. If obtained, the documentation may be shared by the investigator with the independent dermatologist or dermatopathologist and may be requested by the sponsor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure with AE, AE in an infant following exposure via breastfeeding, product complaints with AE, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

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

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

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

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study participants and female partners of male study participants that are identified after initiation of study drug and throughout the study, including the protocol-defined follow-up period, to the Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Appendix 4 for further information regarding protocol-defined follow-up periods.

If the investigator learns of any pregnancy or pregnancy outcomes that occur after the protocol-defined follow-up period has concluded but within 700 days following the last dose of SC GS-6207 (Treatment Groups 1 and 2), or within 60 days following the last oral dose of GS-6207, the investigator should promptly document and report the event to Gilead GLPS.

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

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

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

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

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to the Gilead GLPS 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 GLPS (Treatment Groups 1-4). If the pregnancy occurs after the study has been completed, but within 700 days following the last dose of SC GS-6207, the pregnancy/outcome should be reported directly to Gilead GLPS (Treatment Groups 1-2). Gilead GLPS contact information is as follows: email: PPD and fax: PPD

Pregnancies of female partners of male study participants exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to the Gilead GLPS using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS: fax number PPD or email PPD

Refer to Appendix 4. for Pregnancy Precautions, Definition for Women 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 the Gilead GLPS within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug 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, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

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 instructions on special situation 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.

7.8. Safety Monitoring Committee

Gilead teams periodically review accumulating safety data across completed and ongoing studies within the GS-6207 development program to detect unexpected suspected adverse reactions and clinically important increased rates of AEs, laboratory abnormalities, and previously recognized adverse reactions. If, during the periodic review of safety data from clinical studies, a significant numerical imbalance is observed for an AE across treatment groups based on predefined reporting thresholds, a safety monitoring committee will request to review unblinded safety data and, in collaboration with other safety committees (in line with Gilead's signal management process and unblinding process), determine if any actions are necessary to protect participants involved in the GS-6207 development program. If appropriate and available, the safety monitoring committee would be a data monitoring committee (DMC). If an appropriate DMC is not available, an internal Safety Assessment Committee (SAC), comprised of Gilead employees not involved in the conduct of the study, reviews the data. The membership, responsibilities, conduct, specific activities, and meeting schedule of the unblinded internal SAC will be described in a charter. The blind will be maintained for persons responsible for the ongoing conduct of the study and those responsible for data analysis and interpretation of results at the conclusion of the study.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the efficacy of regimens in PLWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54

The secondary objectives of this study are:

- To evaluate the efficacy of regimens in PLWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80
- To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80
- To evaluate the safety and tolerability of regimens through 28, 38, 54, and 80 weeks of treatment
- To evaluate the PK of GS-6207, BIC, and TAF

CCI [redacted]

8.1.2. Primary Endpoint

The primary endpoint is the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US-FDA-defined snapshot algorithm.

8.1.3. Secondary Endpoint

The secondary endpoints are:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the US-FDA-defined snapshot algorithm

- The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted for DMC analysis, for data to be submitted to regulatory agencies to seek guidance for the overall clinical development program, and to support regulatory filings, etc.

8.2.1.1. Planned Internal Analysis

Prior to the primary analysis (defined in Section 8.2.2), there will be two planned internal analyses. One analysis will be performed after all participants have completed their Week 28 visit or prematurely discontinued study drug. The other analysis will be conducted after all participants have completed their Week 38 visit or prematurely discontinued study drug. Both analyses will be used to support the GS-6207 regulatory filing and the planning of other studies.

After the primary analysis, the Week 80 analysis will be conducted after all participants have completed their Week 80 visit or prematurely discontinued study drug.

8.2.1.2. DMC Analysis

There will be one planned DMC analysis conducted after all participants have completed their Week 16 visit. No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of AEs associated with a study regimen warrant the early termination of the study in the best interest of the participants. No alpha penalty will be applied for the primary analysis of the primary efficacy endpoint given that the study is not adequately powered for a formal efficacy evaluation. Data from this analysis may be used to support the GS-6207 regulatory filing and the planning of other studies.

8.2.2. Primary Analysis

The primary analysis will be conducted after all participants have completed the Week 54 visit or have prematurely discontinued study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis of the primary endpoint will serve as the final analysis for this endpoint.

8.2.3. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses is defined as Full Analysis Set (FAS), which includes all participants who are randomized and receive any dose of study drug. Participants will be grouped according to the treatment to which they are randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as Safety Analysis Set, which includes all participants who are randomized and receive any dose of study drug. Participants who receive treatment other than that intended will be analyzed according to treatment received. All data collected during treatment will be included in the safety summaries.

8.3.1.3. Pharmacokinetics

The primary analysis set for PK analyses is defined for each analyte, which includes all participants who are randomized, receive any dose of study drug, and have at least 1 non-missing postbaseline concentration value for the analyte of interest.

8.3.2. 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 BIC (and any metabolites, as applicable) (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 predose and one-half of the LLOQ for postdose 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 and Baseline Characteristics Analysis

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

Demographic summaries will include age, race, ethnicity, sex, sexual orientation, gender identity, and randomization stratification group.

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

For categorical demographic and baseline characteristics, the Cochran-Mantel-Haenszel (CMH) test will be used to compare across treatment groups. For continuous demographic and baseline characteristics, the 2-sided Kruskal-Wallis test will be used to compare across treatment groups.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US-FDA-defined snapshot algorithm. The primary analysis of the efficacy endpoint will be based on the FAS.

The point estimates and 95% CI for the difference in the response rates between each of the GS-6027-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) will be constructed using normal approximation method, stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL). The nominal p-values will be provided for above mentioned treatment group comparisons using the 2-sided CMH test stratified by the baseline HIV-1 RNA level.

8.5.2. Secondary Analyses

The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80, respectively, will be analyzed using the same methods as for the primary efficacy endpoint.

The changes from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count will be summarized using descriptive statistics. The differences in changes from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count between treatment groups and the associated 95% CIs will be constructed using analysis of variance (ANOVA) models adjusting for the baseline HIV-1 RNA level.

8.6. Safety Analysis

For Treatment Groups 1 and 2, all safety data collected on or after the first dose date will be included. For participants who discontinue from the oral GS-6207, only data collected up to 60 days (approximately 5 times the GS-6207 oral dose half-life) after the last dose of the oral GS-6207 will be included. For Treatment Groups 3 and 4, all safety data collected on or after the first dose date and up to 60 days and 30 days, respectively, after the last dose date will be included. All data will be summarized by treatment according to the study drug received. All collected data will be included in data listings.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory AEs 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. For Treatment Groups 1 and 2, a treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug. For participants in Treatment Groups 1 and 2 who discontinue from the oral GS-6207, only AEs collected up to 60 days (approximately 5 times the GS-6207 oral dose half-life) after the last dose of the oral GS-6207 will be considered treatment emergent. For Treatment Groups 3 and 4, a TEAE will be defined as any adverse event that begins on or after the date of first dose of study drug and up to 60 days and 30 days, respectively, after the last dose date; or any AE leading to study drug discontinuation.

Summaries (number and percentage of participants) of TEAEs (by SOC and PT) will be provided by treatment group. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

Incidence of treatment-emergent laboratory abnormalities will be summarized by treatment group. For Treatment Groups 1 and 2, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time post baseline (and up to 60 days after the last dose date if participants discontinue from the oral GS-6207). For Treatment Groups 3 and 4, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 60 days and 30 days, respectively. 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.

8.6.4. Other Safety Evaluations

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

8.7. Adjustments for Multiplicity

Not applicable.

8.8. Pharmacokinetic Analysis

Plasma concentrations of GS-6207, TAF, and BIC (and metabolites, as applicable) will be summarized by nominal sampling time and treatment using descriptive statistics. Pharmacokinetic 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.

8.9. Biomarker Analysis

Not applicable.

8.10. Sample Size

A sample size of 50 participants in Treatment Groups 1 to 3, respectively, was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 54. A total sample size of 75 participants for each pair of comparisons (ie, between each of the GS-6207-containing regimen groups [Treatment Groups 1 to 3, n = 50] and the B/F/TAF [Treatment group 4, n = 25]) will provide 39% power to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 54. In this sample size and power calculation, it is assumed a response rate is 90.9% (based on pooled data from studies GS-US-380-1489 and GS-US-380-1490) for each treatment group and a non-inferiority margin is 0.12.

8.11. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of efficacy and safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of 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 International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

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

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

9.1.4. Informed Consent

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

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9.1.5. Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB, or laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

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

9.1.6. Study Files and Retention of Records

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

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

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

- Participant identification;
- Documentation that participant meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- 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, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

9.1.7. Case Report Forms

For each participant consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. 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. Data entry should be performed in accordance with the CRF completion guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, 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 study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator 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 study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries in the CRF/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 Gilead 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 participants, appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGMENT

A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination with Other Antiretroviral Agents in People Living with HIV

GS-US-200-4334, Amendment 4 04 February 2022

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

	[See appended electronic signature]
Name (Printed) Executive Director, Clinical Research	Signature
[See appended electronic signature]	
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

Prot GS-US-200-4334 amd-4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	07-Feb-2022 10:36:27

Appendix 2. Study Procedures Table

	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	Oral Bridging Visits[d]	30, 90, 180 Day Follow-Up[e]	Early Termination[f]
Written Informed Consent	X														
Obtain demographic information	X														
Medical History	X														
Complete Physical Examination	X	X				X	X[g]		X		X				X
Symptom-Directed Physical Examination			X		X		X[h]	X		X		X	X	X	
Vital Signs[i] (including weight)	X	X	X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (supine)	X														
Height	X														
Hematology[j], Chemistry[k], Lipid panel[l], Urinalysis and Urine Chemistry[m], CD4+ Cell Count	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

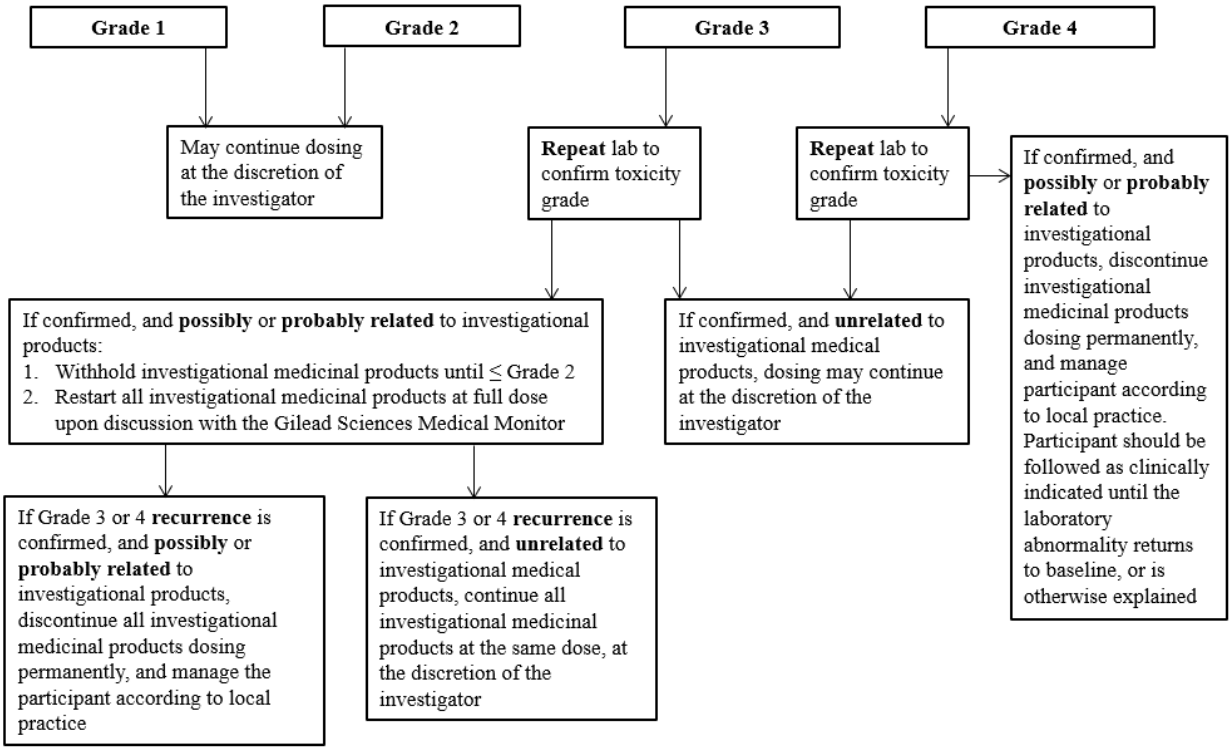
	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	Oral Bridging Visits[d]	30, 90, 180 Day Follow-Up[e]	Early Termination[f]
Serum Pregnancy Test[n]	X														X
Serum FSH[o]	X														
Urine Pregnancy Test[n]		X	X		X	X	X	X	X	X	X	X	X	X	X
HBV, HCV Testing	X														
HIV-1 Genotyping/ Phenotyping	X														
Plasma HIV-1 RNA	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
PK Plasma Collection[p]		X	X		X	X	X	X	X	X	X	X	X		
CCI															
Oral GS-6207 Dispensation[t]		X	X		X		X	X	X	X	X	X	X		

	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	Oral Bridging Visits[d]	30, 90, 180 Day Follow-Up[e]	Early Termination[f]
Subcutaneous GS-6207 Administration[u]						X	X		X		X	X			
F/TAF Dispensation[v]		X					X	X	X	X	X	X			
TAF Dispensation[w]							X	X	X	X	X	X			
Bictegravir Dispensation[x]							X	X	X	X	X	X			
B/F/TAF Dispensation[y]		X					X	X	X	X					
Study Drug Accountability		X	X		X	X	X	X	X	X	X	X			
QoL Administration[z]		X				X	X		X		X				
Injection Site Reaction Assessment Worksheet[aa]						X	X		X		X				
Adverse Events/ Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X

a Screening evaluations must be completed within 30 days prior to Day 1
b Day 1 tests and procedures must be completed prior to administration of the dose of study drug. Participants must begin dosing on the same day as Day 1
c Assessments will be performed post Week 80 (Week 90, Week 106, Week 116, Week 132, Week 142) and will continue to alternate between every 10 weeks and every 16 weeks with the visit window ±6 days.
d Only applicable to participants who require oral weekly bridging if an SC injection of GS-6207 cannot be administered for any reason within the protocol visit window.
e Participants may be required to return to the clinic for a 30, 90 and 180-Day Follow-Up Visit after Early Termination visit as noted in Section 6.4.1

f Within 72 hours of permanently discontinuing study. Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care and refer participant to an appropriate HIV treatment facility.
g Complete physical exam is only required at Week 28
h Symptom directed physical to be completed at Weeks 4, 10, 16, and 22, as necessary
i Vital signs – blood pressure, pulse, respiration rate, temperature, and weight
j Hematology: CBC with differential and platelet count
k Chemistries: Alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, and uric acid. eGFR according to the Cockcroft-Gault formula
l Fasting is not required for the lipid panel
m 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
n Women will have a serum test performed at Screening. Urine pregnancy test will only be done for women of childbearing potential. In Treatment Groups 1 and 2, urine pregnancy tests should be confirmed to be negative prior to subcutaneous GS-6207 administration. If any pregnancy test is positive, study drug should be immediately interrupted, and participant should come to the site for serum pregnancy test.
o FSH test is required for women who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
p PK collection: For Treatment Groups 1 and 2, plasma PK sampling will occur relative to dosing of GS-6207 at Days 1, 2 and 8 predose (within 30 minutes of dosing) and a single timed PK sample between 1 and 6 hours postdose. CCI [redacted] At Day 15 and all visits with SC GS-6207, a single predose PK sample will be collected. Starting at Week 4 and at all visits without SC GS-6207, 6207 including the Oral Bridging visits, if applicable, a single anytime PK sample will be collected. PK sampling will continue at visits past Week 80.
For Treatment Groups 3 and 4 participants, starting at Day 1, a single anytime PK sample will be collected at all study visits.
[redacted]
t Treatment Group 1 and 2 oral GS-6207 lead in at Day 1, Day 2 and Day 8. Treatment Group 3 will receive oral GS-6207 lead in at Days 1 and 2 and will begin oral daily GS-6207 at Day 3.
u Treatment Group 1 and 2 Subcutaneous administration at Day 15 and every 26 weeks
v Treatment Group 1, 2, and 3 F/TAF once daily for 28 weeks starting at Day 1. Treatment Group 3 participants will continue F/TAF until study completion.
w Treatment Group 1 daily oral TAF to be initiated at Week 28
x Treatment Group 2 daily oral BIC to be initiated at Week 28
y Treatment Group 4 daily oral B/F/TAF
z Prior to completion of other study procedures, participants will complete HIVTSQ12, HIVDQoL, and EQ-ED-5L at Day 1 (except HIVTSQ12), Day 15 (HIVTSQ12 only), Week 4, Week 28, Week 54, Week 80. Injection Acceptability Scale and Numeric Pain Rating Scale to be completed at Day 15, Weeks 28, 54 and 80 (for Treatment Groups 1 and 2 participants only) after SC GS-6207 administration and completion of other study procedures.
aa Provide Injection Site Reaction Assessment Worksheet and instruct the participants to measure and report injection site reactions following the administration of the subcutaneous injections (for Treatment Group 1 and 2 participants only)

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. Pregnancy Precautions, Definition for Women of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant is considered a woman of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. No documentation of Tanner stage will be required unless the participant is considered to be prepubescent.

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 < 54 years of 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.

For the purpose of this study, permanent sterilization is hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a woman of any age. Tubal ligation is not considered permanent sterilization.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Born Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Nonclinical toxicity studies of GS-6207 have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of GS-6207 in pregnant women. Based on in vitro and in vivo drug–drug interaction liability assessments, a clinically significant drug-drug interaction with GS-6207 and hormonal contraceptives is not expected; an oral contraception drug-drug interaction study was not done.

No adequate and well-controlled study of F/TAF, FTC, or TAF has been conducted in pregnant women. There is an ongoing clinical study of B/F/TAF in pregnant women. Non-clinical toxicity studies of BIC, FTC, and TAF have demonstrated no adverse effect on fertility or embryo-fetal development. Neither BIC, FTC nor TAF are considered to be genotoxic. Please refer to the latest version of the investigator's brochures for additional information.

b. Contraception Requirements for Female Born Participants of Childbearing Potential

The inclusion of female born participants of childbearing potential requires using at least an acceptable effective contraceptive. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the Day 1 visit prior to the dose of study drug. Pregnancy tests will be performed as defined by the study procedures 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 also applicable for female born participants of childbearing potential with infrequent or irregular periods.

Duration of contraception for female born participants of childbearing potential enrolled in this clinical trial should start from Screening visits until 60 days after the last dose of oral study drug or 700 days following the last dose of subcutaneous study drug, whichever is later, as applicable.

Female born participants of childbearing potential must agree to 1 of the following contraceptive methods:

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

Or

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

  — Hormonal and non-hormonal intrauterine device (IUD)

  — Bilateral tubal occlusion (upon medical assessment of surgical success)

  — Vasectomy in the male born partner (upon medical assessment of surgical success)

Or

Female born participants who initiate use of a hormonal contraceptive > 7 days after onset of menses as one of their birth control methods should use additional back-up contraception (eg, condoms) or avoid sexual intercourse for 7 days. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

— Hormonal Methods

  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

— Barrier methods

- Male condom (with or without spermicide)
- Female condom (with or without spermicide)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female born participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Born Participants

No contraception measures are needed.

Condoms should be used for all sexual activity including oral, vaginal, and anal sexual contact to decrease the risk of transmission of HIV and other sexually transmitted diseases.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Female born participants who are pregnant or suspect they are pregnant will be instructed to notify the investigator at any time during the study, including the protocol-defined follow-up period (Treatment Groups 1-4), and if they become pregnant within 700 days following the last dose of SC GS-6207 (Treatment Groups 1 and 2) or within 60 days following last dose of oral GS-6207. Participants who become pregnant or who suspect that they are pregnant during the study should discontinue study drug(s) immediately.

Male participants whose partner has become pregnant or suspects she is pregnant during the study, including the protocol-defined post-treatment follow-up period, 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 5. Pandemic Risk Assessment and Mitigation Plan

In the event of an ongoing pandemic (such as COVID-19), potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

- Study drug supplies to participants and sites:

  — Oral GS-6207 (600 mg and 300 mg doses) and SC GS-6207 study drug administration must occur at the study site. Dispensation of other oral study drug(s) must occur at the study site. Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to stay on the study drug as planned per protocol.

    Mitigation plan: Oral study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator (PI). A virtual visit must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by local ethic committee (EC)/institutional review boards (IRBs)/Regulatory Authority as applicable and with sponsor's approval. If a participant is attending a visit in-clinic and there is a risk that the next visit may not occur in-clinic, the site may dispense an additional bottle(s) of oral study drug(s) to the participant in anticipation of the missed visit. In such cases, a virtual visit will be performed if the participant is not able to come for in-person visit at the clinic. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments.

  — Study drug shortage at site level.

    Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

- Participant safety monitoring and follow-up:

  — Participants cannot come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For participants who cannot come to the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

- Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs) and follow-up on any unresolved AE/SAEs.
- Review current list of concomitant medications and document any new concomitant medications.
- Review any changes in medical history.
- Confirm participant's oral study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above. GS-6207 SC dose can only be given at site. If participant is not able to come for in-person visit to receive GS-6207 SC dose at their scheduled visit, Sponsor should be notified receive guidance on next steps.
- Remind participant to maintain current oral dosing and to keep all dispensed study drug kits for return at the next on-site visit.

— Safety blood draws & central laboratory analysis cannot be done.

Mitigation plan: Local labs may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol per PI discretion. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly.

— Participants are unable to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

- Protocol and monitoring compliance:

— Protocol deviations in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure at scheduled visit, the visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation (PD). Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the e-case report form (CRF) and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a PD related to the pandemic.

— On-site monitoring visit is not feasible.

Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), study drug accountability, or protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution (remote SDV not allowed). The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

- Missing data and data integrity:

— Increased number of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Virtual visits should be documented in the participant's source documents. For any completed virtual visits, associated data will be entered in EDC and a general comment will be added noting that the visit was completed virtually due to pandemic.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks would be considered mitigated with the implementation of these measures, the expected benefit risk assessment of study drug(s) in study participants remains unchanged.