CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living with HIV-1 Infection with Multidrug Resistance
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: EudraCT Number: Clinical Trials.gov Identifier:	136260 2019-003814-16 04150068
Indication:	HIV-1 Infection
Protocol ID:	GS-US-200-4625
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 September 2019 Amendment 1: 18 December 2019 Amendment 2: 01 September 2020

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

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long-Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living with HIV-1 Infection with Multidrug Resistance
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	136260 2019-003814-16 04150068
Study Centers Planned:	Approximately 75 centers globally
Objectives:	The primary objective of this study is: • To evaluate the antiviral activity of GS-6207 (Lenacapavir, LEN) administered as an add-on to a failing regimen (functional monotherapy) for people living with HIV (PLWH) with multi-drug resistance as determined by the proportion of participants achieving at least 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period The secondary objective of this study is: • To evaluate the safety and efficacy of GS-6207 in combination with an optimized background regimen (OBR) at Weeks 26 and 52 CCI [redacted]

Study Design:

This is a global multicenter study of GS-6207 together with an OBR in people living with HIV with multidrug resistant infection.

Participants who complete a Screening visit will return to the clinic between 14 and 30 days after the Screening visit, for a Cohort Selection visit. HIV-1 RNA results from this Cohort Selection visit will be used to determine whether eligible participants will participate in Cohort 1 or Cohort 2.

Cohort 1 (n 36)

Functional Monotherapy Period

Eligible participants with a < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and HIV-1 RNA ≥ 400 copies/mL at the Cohort Selection visit will be randomized, in a blinded fashion, in a 2:1 ratio to receive either oral GS-6207 or placebo to match GS-6207 for 14 days. Treatment assignment will be blinded to the Sponsor, participants, investigators and study staff at the site. Functional Monotherapy will be assessed while participants continue their failing regimen.

After each participant completes the Functional Monotherapy Period, their treatment assignment will be unblinded.

Maintenance Period

Participants who were randomized to receive oral GS-6207 will receive subcutaneous (SC) GS-6207 and initiate their OBR on Day 1 SC (14 days after the first dose of oral GS-6207) **(Cohort 1A)**.

Participants who were randomized to receive placebo will receive oral GS-6207 and initiate their OBR on Day 15 **(Cohort 1B)**. They will receive SC GS-6207 at Day 1 SC (eg, 14 days after the first dose of oral GS-6207) while continuing their OBR.

After the Day 1 SC visit, all Cohort 1 participants will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52 (study visits Week X are identified by the number of weeks that have elapsed since the Day 1 SC visit when GS-6207 is first administered by injection). Participants will receive their subsequent SC GS-6207 injection at the Week 26 visit. At the Week 52 visit, participants will be given an option to receive SC GS-6207 injection and continue

on the study to receive SC GS-6207 injections every 6 months (26 weeks).

Cohort 2 (n 64)

Oral Lead-in Period

Participants will be enrolled into Cohort 2 if Cohort 1 is fully enrolled or if they do not meet the criteria for randomization in Cohort 1 (ie, they had ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and/or HIV-1 RNA < 400 copies/mL at the Cohort Selection visit). All Cohort 2 participants will receive oral GS-6207 for 14 days starting at Day 1. Participants will initiate an OBR on Day 1.

Maintenance Period

At Day 1 SC (ie, 14 days after the first dose of oral GS-6207), participants will receive SC GS-6207 and will continue their OBR. After the Day 1 SC visit, participants will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52 (study visits Week X identified by the number of weeks that have elapsed since the Day 1 SC visit when GS-6207 is first administered by injection). Participants will receive their subsequent SC GS-6207 injection at the Week 26 visit. At the Week 52 visit, participants will be given an option to receive SC GS-6207 injection and continue the study to receive SC GS-6207 injections every 6 months (26 weeks).

Number of Participants Planned:	Approximately 100 participants may be enrolled in this study. 36 participants will be enrolled in Cohort 1. Up to 64 participants may be enrolled in Cohort 2.
Target Population:	Heavily treatment experienced adults and adolescent PLWH with resistance to ≥ 2 antiretroviral medications from each of ≥ 3 of the 4 main classes of antiretroviral medication and plasma HIV-1 RNA ≥ 400 copies/mL at Screening while taking a failing regimen. Adolescent participants will be enrolled only at sites in North America and Dominican Republic.
Duration of Treatment:	Duration of treatment is at least 54 weeks. CCI [redacted] Participants willing to continue the study beyond Week 52 will receive SC GS-6207 927 mg every 6 months (26 weeks) starting at

	Week 52 visit, while continuing their OBR, until the product becomes accessible to participants through an access program or until Gilead Sciences elects to discontinue the study in the country. Participants who decide not to receive SC GS-6207 at Week 52 and not to continue the study will complete the study at Week 52 visit. Participants who decide to discontinue SC GS-6207 early and do not wish to continue to attend study visits through the Week 52 visit or the next scheduled SC dosing visit will complete 30-Day, 90-Day and 180-Day Follow Up visits after the Early Termination Visit. The 180-Day Follow Up may be conducted via a phone call per the investigator's discretion.
Diagnosis and Main Eligibility Criteria:	People living with HIV who meet the following criteria: • Adults and adolescents aged ≥ 12 and weighing ≥ 35 kg • Are receiving a stable failing regimen for > 8 weeks before Screening and are willing to continue that regimen until Day 1. Cohort 1 participants should be willing to continue their failing regimen until Day 14 • Have HIV-1 RNA ≥ 400 copies/mL at Screening • Have resistance to ≥ 2 antiretroviral medications from each of ≥ 3 of the 4 main classes of antiretroviral medications (NRTI, NNRTI, PI, INSTI). Resistance to FTC or 3TC associated with the presence of the M184V/I RT mutation cannot be used for the purpose of determining eligibility for this criterion • Have ≤ 2 fully active antiretroviral remaining from the 4 main classes that can be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant • Able and willing to receive an OBR together with GS-6207
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 will be performed, and HBV and HCV serologies will be analyzed. Laboratory samples for resistance analysis will be collected. Analysis of the

participant's HIV-1 resistance to support eligibility will be completed.

Participants who complete a Screening visit will return to the clinic between 14 and 30 days after the Screening visit for a Cohort Selection visit. HIV-1 RNA results from this follow-up visit will be used to randomize participants in Cohort 1 or enroll them in Cohort 2.

- Cohort 1 (n 36): Participants in Cohort 1 will be randomized to receive oral GS-6207 or placebo to match GS-6207 during the Functional Monotherapy Period while continuing their failing regimen. During the Maintenance Period, they will receive SC GS-6207 and an OBR.
- Cohort 2 (n 64): Participants in Cohort 2 will be enrolled to receive oral GS-6207 and an OBR in the Oral Lead-in Period. During the Maintenance Period they will receive SC GS-6207 and continue their OBR.

Functional Monotherapy Period (Cohort 1 only)

Participants with both < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and HIV-1 RNA ≥ 400 copies/ml at the Cohort Selection visit will be randomized to receive oral GS-6207 or placebo to match GS-6207 while continuing their failing regimen. Sites, participants and Sponsor will be blinded to the participant treatment assignment.

Participants will visit the clinic on Days 1, 2, 5 (±1) (if possible) and 8. On Day 1 before dosing, baseline assessments will be conducted including adverse events (AEs), concomitant medications, laboratory assessments and physical examinations as detailed in the Study Procedures Table (Appendix 2). After completion of the assessments, the participant will receive oral GS-6207 600 mg, 600 mg, and 300 mg or placebo to match GS-6207 on Days 1, 2, and 8 respectively.

After each participant completes the Functional Monotherapy Period, their treatment assignment will be unblinded.

Maintenance Period (Cohort 1A)

Participants who received oral GS-6207 during the Functional Monotherapy Period will receive SC GS-6207 927 mg and initiate an OBR at the Day 1 SC visit (14 days after the first dose of oral GS-6207). They will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52. Participants will receive their subsequent SC GS-6207 injection at the Week 26 visit.

At the Week 52 visit, participants will be given an option to receive SC GS-6207 injection and continue on the study to receive SC GS-6207 injections every 6 months (26 weeks).

Maintenance Period (Cohort 1B)

Participants who received placebo to match GS-6207 during the Functional Monotherapy Period (Day 1 to Day 14) will visit the clinic on Days 15, 16, 19 (±1) (if possible) and 22. They will receive oral GS-6207 600 mg and initiate their OBR on Day 15. After completing study visit assessments, participants will receive additional oral GS-6207 600 mg and 300 mg on Days 16 and Day 22, respectively.

Participants will receive SC GS-6207 927 mg at the Day 1 SC visit (14 days after the first dose of oral GS-6207) while continuing their OBR. They will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52. Participants will receive their subsequent SC GS-6207 927 mg injection at the Week 26 visit.

Oral Lead-in (Cohort 2 only)

Participants will be enrolled into Cohort 2 if Cohort 1 is fully enrolled or if they do not meet the criteria for randomization in Cohort 1 (ie, they had ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and/or HIV-1 RNA < 400 copies/mL at the Cohort Selection visit). Participants will be enrolled in Cohort 2 to initiate oral GS-6207. Participants will initiate their OBR on Day 1.

Participants will visit the clinic on Days 1, 2, 5 (±1) and 8 during the Oral Lead-in Period.

On Day 1 before dosing, baseline assessments will be conducted including AEs, concomitant medications, laboratory tests and physical examinations as detailed in the Study Procedures Table (Appendix 2). After completion of the assessments, the participant will receive oral GS-6207 600 mg, 600 mg, and 300 mg on Days 1, 2, and 8, respectively.

Maintenance Period (Cohort 2)

Participants will receive SC GS-6207 927 mg at Day 1 SC visit (14 days after the first dose of oral GS-6207) while continuing their OBR. They will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52. Participants will receive

their subsequent SC GS-6207 927 mg injection at the Week 26 visit.

Cohort 1 and Cohort 2

CCI [redacted] articipants willing to continue beyond Week 52 visit will receive SC GS-6207 927 mg every 6 months (26 weeks) starting at Week 52 visit.

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

Resistance Analysis:

Plasma samples for genotypic and phenotypic testing of HIV-1 will be collected in accordance with the Study Procedures Table (Appendix 2). Screening results and/or historic HIV-1 resistance reports will be used to determine eligibility and to help construct the OBR.

CCI [redacted]

CCI

[redacted]

Patient reported outcomes (PROs): Participants ≥ 18 years of age will complete the following, if available**:**

- Symptoms Distress Module, Short Form Health Survey (SF-36), EQ-5D-5L at Day 1, Weeks 4, 16, 26 and 52
- The Numeric Pain Rating Scale at Day 1 SC, Weeks 26 and 52

Test Product, Dose, and Mode of Administration:	Oral GS-6207 and SC GS-6207 injection. Study drug will be administered without regard to food.
Reference Therapy, Dose, and Mode of Administration:	Placebo to match GS-6207 (during the randomized Functional Monotherapy Period) None (during the Maintenance Period)

Criteria for Evaluation:

Safety: Incidence of treatment-emergent AEs and clinical laboratory abnormalities

Efficacy: The primary endpoint is:

- The proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ copies/ml reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period.

The secondary endpoint is:

- The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 visits based on the US FDA-defined snapshot algorithm.

Statistical Methods:

The primary efficacy analysis is to compare the proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period. The p-value and 95% confidence interval for the difference in response rates between two treatment groups (GS-6207 in Cohort 1A and placebo in Cohort 1B) will be estimated and constructed based on an unconditional exact method using 2 invert 1-sided tests with an alpha level at 0.05.

The proportion of participants in Cohort 1 with HIV-1 RNA < 50 copies/mL and < 200 copies/mL based on the US FDA-defined snapshot algorithm at Weeks 26 and 52 will be summarized using descriptive statistics.

Incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities will be summarized.

Data from Cohort 2 will be summarized descriptively.

A total of 36 participants in Cohort 1 will provide at least 90% power to detect a 60% difference in the proportion of participants achieving a ≥ 0.5 $\log_{10}$ reduction from baseline at the end of the Functional Monotherapy Period between treatment groups (GS-6207 in Cohort 1A and placebo in Cohort 1B). In this sample size and power computation, it is assumed that 70% and 10% of participants achieve a ≥ 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA in the GS-6207 group (Cohort 1A) and the placebo group (Cohort 1B) (based on data from Trogarzo Phase 3 TMB-301 study {Emu 2018}), respectively, and the Fisher exact test is conducted at 2-sided significant level of 0.05.

A total sample size of 36 participants from Cohort 1A and Cohort 1B will provide reasonable assessment of safety for at least 26 weeks of treatment in heavily treatment experienced participants.

The external multidisciplinary Data Monitoring Committee will review the progress, efficacy, and safety data after all participants in Cohort 1 have completed 14 days of assessment in the Functional Monotherapy Period or discontinued the study drug. Further enrollment will be stopped if 50% or more of the participants in the GS-6207 group fail to achieve at least 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period. The decision whether to continue with the study and

	the development of GS-6207 will be based on the magnitude of the HIV-1 RNA decline at the end of the Functional Monotherapy Period.

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}
%CV	percentage coefficient of variation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
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
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
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
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization
CSR	clinical study report
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	Electrocardiogram
EFV	Efavirenz
eCRF	electronic case report form
EDC	electronic data capture
EudraCT	European Clinical Trials Database
eSAE	electronic serious adverse event
ET	early termination
EU	European Union

FAM	Famotidine
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GLPS	Global Patient Safety formerly known as Pharmacovigilance and Epidemiology (PVE)
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBSAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus, type 1
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IND	investigational new drug (application)
IRB	institutional review board
IUD	intrauterine device
LEN	Lenacapavir
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MDR	multi-drug resistance
MDZ	Midazolam
NaS	Sodium salt
OBR	Optimized Background Regimen
PD	pharmacodynamic(s)
PG	Pharmacogenomics
PI	principal investigator
PIT	Pitavastatin
PK	pharmacokinetic(s)
PLWH	people living with HIV
PRO	Patient Reported Outcomes
GLPS	Global Patient Safety (formerly Pharmacovigilance and Epidemiology (PVE))
QA	quality assurance
QD	Once Daily

RIF	Rifampin
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	suboptimal virologic response
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
$t_{1/2}$	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 and 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 (eg, 2 NRTIs plus a third agent) to suppress viral replication to below detectable limits, increase CD4 cell counts, and delay disease progression.

While combination ARV therapy for the treatment of HIV-1 infection is efficacious and well tolerated, these agents need to be taken every day and require near perfect adherence to minimize the emergence of drug resistant variants. In addition, "treatment fatigue" can occur, defined as "decreased desire and motivation to maintain vigilance in adhering to a treatment regimen" among 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 (eg, long acting drug products), thereby providing an alternative treatment option for PLWH.

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 studies GS-US-200-4072 received injections of a 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-Sep-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 Single and Multiple Ascending Doses [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 Table 1-3.

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)**

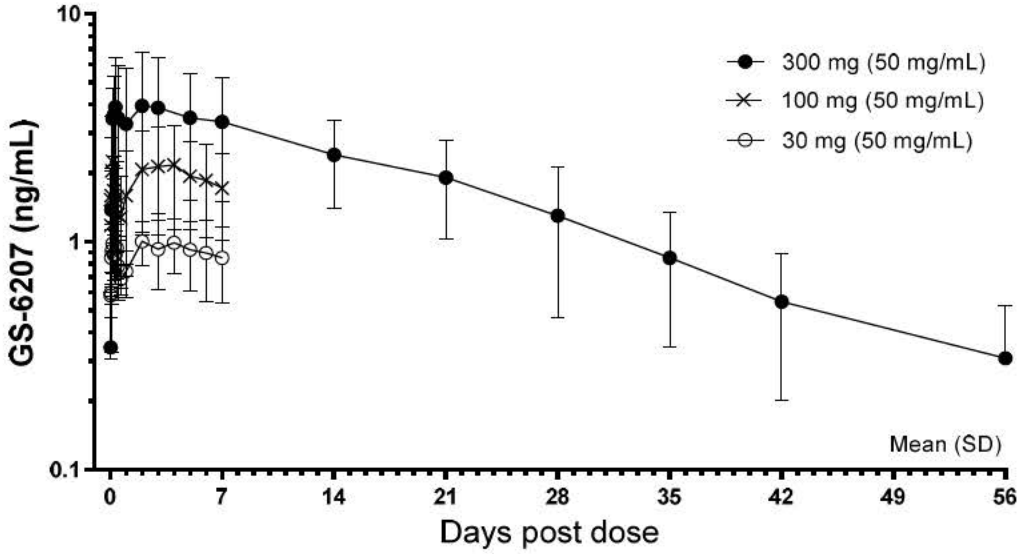


Table 1-2. **GS-US-200-4071: Preliminary Plasma Pharmacokinetic Parameters of GS-6207 Following Single Dose Oral Administration of 50 mg/mL Solution in Capsule (N 8 per cohort)**

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)
$\%AUC_{exp}$	ND	ND	11.6 (61.0)
$AUC_{0\text{-}24}$ (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] AUClast calculated through Day 7 post dose for Cohorts 1 and 2 and through last currently available timepoint for Cohort 5; $AUC_{0\text{-}24hr}$ 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)
$AUC_{0\text{-}24hr}$ (hr*ng/mL)	232 (17.9)	843 (56.5)

Pharmacokinetic parameters are presented as Mean (%CV), and shown to 3 significant digits; $AUC_{0\text{-}24hr}$ AUC from time zero through 24 hours post dose; †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 post-dose. Based on preliminary PK data, GS-6207 exposures increased in a less than dose-proportional manner over the range of 50 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 Fasted Administration of Oral GS-6207 Tablets (N 8/cohort)**

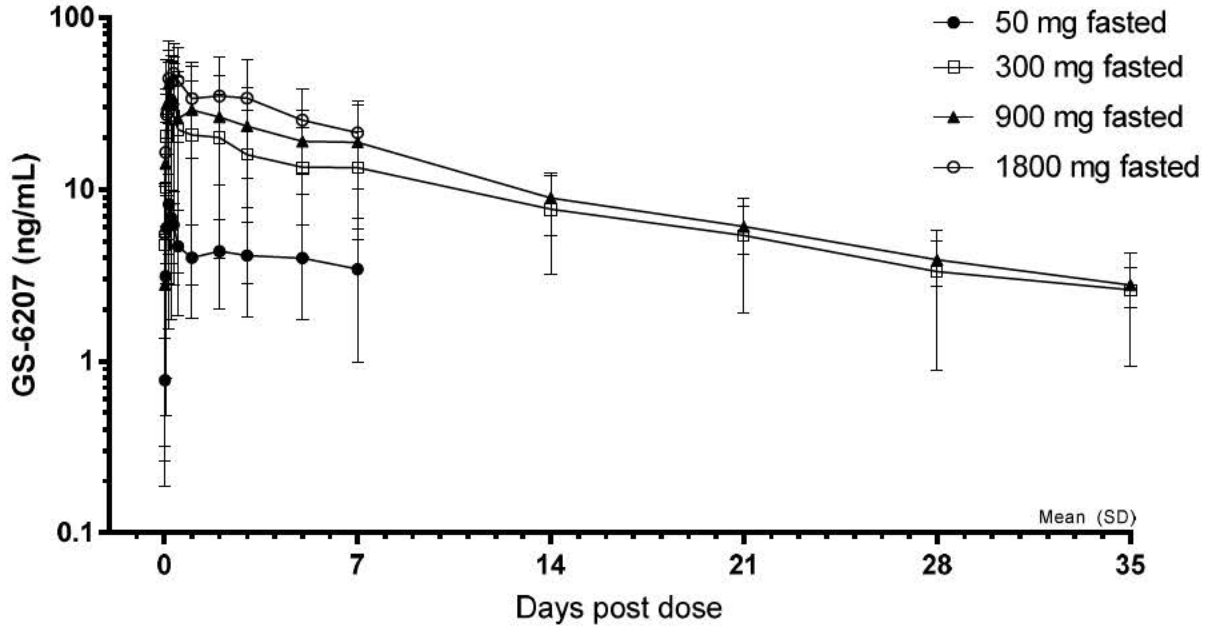


Figure 1-3. **GS-US-200-4071: Preliminary Mean (SD) GS-6207 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-6207 300 mg Tablets, Administered Fasted or with a High Fat or Low Fat Meal (N 8/cohort)**

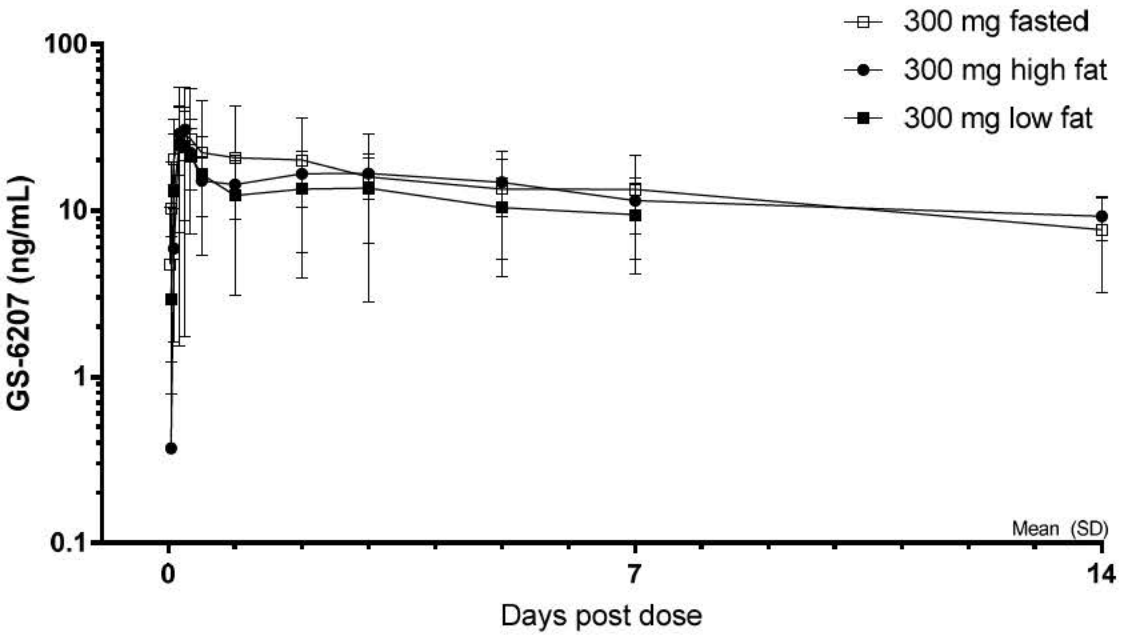


Table 1-4. **GS-US-200-4071: Preliminary Plasma Pharmacokinetic Parameters Following Single Dose Oral Administration of GS-6207 Tablets, Fasted, or Following a High or Low Fat Meal (N 8 per cohort)**

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 AUC0 D8 calculated through Day 8 post dose

Safety Results

Safety data as of 03-Sep-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, 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-Sep-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

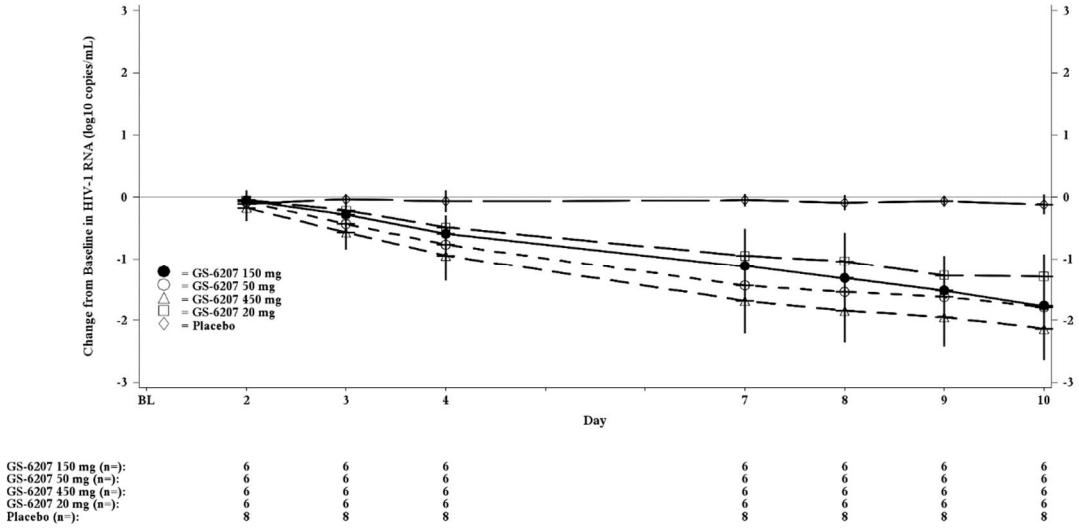
As of 25 July 2019, 32 participants have been randomized and received a single dose of SC GS-6207 or placebo. All participants are continuing in study follow up. The median duration of follow-up (number of days between Day 1 and the last study date) ranged from 38 to 199 days across the 4 cohorts.

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 to 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, 50, 150, 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 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)



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 (IQ 1.1, 3.3, and 9.9, for the 50, 150, and 450 mg doses, respectively).

Safety Results

As of 25 Jul 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 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 electrocardiogram (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 of GS-6207. As of 17 November 2019, a total of 21 unique participants have received GS-6207 or placebo as a 1-hour intravenous 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 potential of GS-6207. Available preliminary data for GS-6207 capsules administered in combination with known strong cytochrome P450 enzyme (CYP)3A/Pglycoprotein (P-gp) inhibitors, darunavir (DRV)/cobicistat (COBI) and COBI, or GS-6207 tablets administered in combination with a strong CYP3A/UGT/Pgp inducer, rifampin (RIF), an acid reducing agent, famotidine (FAM), and OATP, Breast Cancer Resistance Protein (BCRP), P-gp or CYP3A substrates, pitavastatin (PIT), 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 initiated.

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 once daily (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. PK 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 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/COBI 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 two-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/Pgp inhibitors. Accordingly, the use of strong CYP3A and Pgp 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 (150mg 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 1-5). 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 the 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, administration of FAM and other acid reducing agents with GS-6207 is therefore permitted.

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)	6360 (52.9)
$\%AUC_{exp}$	30.0 (24.6)	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]	270.0 (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 Tmax, t1/2, and Tlast, 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 25; b N 24; %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 = 30)
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 25; b N 24; %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 = 30)
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)

a N 25; b N 24; %CV percentage coefficient of variation; TAF tenofovir alafenamide; TFV tenofovir; 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.

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 Pgp 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

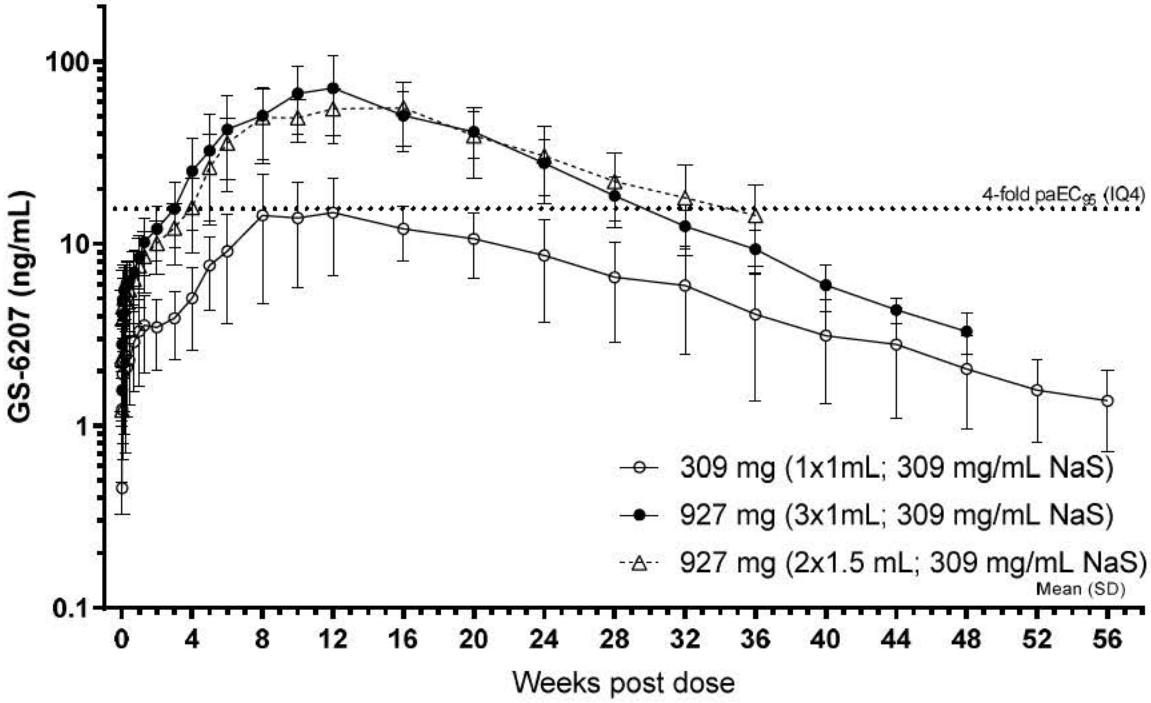
GS-US-200-4538 is an ongoing, blinded Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single ascending SC doses of GS-6207 solution formulations. As of 28 August 2019, 30 unique participants across 3 dosing cohorts have received single doses of either SC GS-6207 injection, 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 dose of SC GS-6207 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 (Figure 1-5., Table 1-11.). Preliminary PK data through 20 weeks post dose 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 SC GS-6207 Injection, 309 mg/mL (NaS) (N 8 per cohort)



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

Table 1-11. Preliminary PK parameters for GS-6207 Injection, 309 mg/mL (NaS)

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

PK parameters presented to 3 significant figures as mean (%CV), except T_{max} and $T_{1/2}$: median (Q1, Q3). NC = not calculated due to insufficient data at this time

Safety Results

In a preliminary blinded review of safety data as of 28 August 2019 30 participants received SC GS-6207 injection, 309 mg/mL. No deaths or Grade 4 AEs were 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.

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)

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.

1.3. 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.

Some treatment-experienced (TE) PLWH eventually lose virologic, immunologic, or clinical benefit from their current regimens. People living with HIV with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {Department of Health and Human Services (DHHS) 2013}, {Lundgren 2013}, {Thompson 2010}, {U. S. Department of Health and Human Services 2015}, {Williams 2014}. These challenges are also relevant for adolescents particularly those with perinatal HIV-1 transmission (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4901868/)

Developing safe and effective therapies for heavily TE PLWH with multi-drug resistant (MDR) HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression. In all PLWH, the ideal goal of therapy remains complete and durable viral suppression.

1.4. Rationale for Dose Selection of 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 TN and TE but CAI-naïve PLWH, as well as PK and safety data from the two Phase 1 studies in healthy volunteers (Study GS-US-200-4538 and Study 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 to 450 mg was 1.8 to 2.2 $\log_{10}$ copies/mL. 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 dose range of single doses of 50 to 450 mg. At these doses, mean (% CV) GS-6207 concentrations on Day 10 were 1.1 to 9.9 fold higher (eg, IQ 1.1 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).

Phenotypic analyses of GS-6207 susceptibility in patient derived isolates indicate that isolates from TN and heavily TE PLWH have a similar in vitro profile, suggesting similar GS-6207 antiviral activity should be observed in the heavily TE patient population compared to the TN patient population.

Based on these data, a concentration of 15.5 ng/mL (corresponding to an IQ of 4 based on paEC95 from MT-4 cells), is anticipated to provide antiviral activity in the HTE population.

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. The proposed regimen targets an exposure whereby the lower bound of the 90% confidence interval (90% CI) of the C_{trough} is 4-fold higher than the $paEC_{95}$ (ie, IQ4) within a few days of dosing initiation, at Day 14 (end of Functional Monotherapy Period), and at end of the dosing interval (q26 weeks).

As described in Section 1.2.2.5, the GS-6207 SC solution formulation exhibits a slow initial release necessitating an oral PK load regimen prior to the first SC injection. In Study GS-US-200-4625, to achieve IQ4 within a few days of dosing and to maintain target concentrations through the Functional Monotherapy Period, participants will receive oral tablet doses of GS-6207 600 mg on Days 1 and 2 and an oral tablet dose of GS-6207 300 mg on Day 8.

Upon completion of the Functional Monotherapy Period, participants will receive GS-6207 927 mg SC (309 mg/mL), followed by SC doses of GS-6207 927 mg administered every 6 months (every 26 weeks), along with the optimized background regimen (OBR). This regimen

is projected to achieve target exposures of GS-6207 within a few days of initiation and to maintain them through the 26 weeks dosing interval.

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.

1.5. 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. Although not specifically evaluated yet, adolescents living with HIV are expected to have similar safety profile as adult PLWH; no additional safety monitoring is required for adolescent participants and no dose adjustments are required. Strategies to mitigate any potential risks include close monitoring of laboratory 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 subtherapeutic concentrations of GS-6207 if dosing is stopped which could lead to HIV-1 developing resistance to GS-6207. Strategies to mitigate any potential risks include initiation of an OBR within 15 days of starting GS-6207 (Cohort 1) or co-initiation of GS-6207 and an OBR (Cohort 2).

PLWH are eligible for participation in this study if they are highly treatment experienced with limited therapeutic options from the 4 main classes of ARV agents and inability to construct a fully active ARV regimen. GS-6207 offers the potential benefit to construct a highly active regimen able to suppress HIV-1 replication, restoring or preserving immunologic function, and averting disease progression to AIDS. 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.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the antiviral activity of GS-6207 (Lenacapavir, LEN) administered as an add-on to a failing regimen (functional monotherapy) for PLWH with MDR as determined by the proportion of participants achieving at least 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period

The secondary objective of this study is:

- To evaluate the safety and efficacy of GS-6207 in combination with an optimized background regimen (OBR) at Weeks 26 and 52

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ copies/ml reduction from baseline in HIV-1 RNA at the end of Functional Monotherapy Period

The secondary endpoint of this study is:

- The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 treatment based on the US FDA-defined snapshot algorithm

3.2. Study Design

This is a randomized and placebo-controlled multicenter study of GS-6207 in PLWH. Eligible participants will be enrolled in either of two cohorts.

Participants who complete a Screening visit will return to the clinic between 14 and 30 days after the Screening visit, for a Cohort Selection visit. HIV-1 RNA results from this Cohort Selection visit will be used to randomize the participant in Cohort 1 or enroll them in Cohort 2. Once enrollment in Cohort 1 is complete, the Cohort Selection visit will not be required.

Cohort 1 (n 36)

Functional Monotherapy Period

Eligible participants with both < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and HIV-1 RNA ≥ 400 copies/mL at the Cohort Selection visit will be randomized, in a blinded fashion, in a 2:1 ratio to either receive oral GS-6207 or placebo to match GS-6207 for 14 days. The Sponsor, participants and site staff will be blinded to the treatment assignment. Functional monotherapy will be assessed while participants continue their failing regimen.

After each participant completes the Functional Monotherapy Period, their treatment assignment will be unblinded.

Maintenance Period

Participants who were randomized to receive oral GS-6207 will receive subcutaneous (SC) GS-6207 and initiate their OBR on Day 1 SC (14 days after the first dose of oral GS-6207) **(Cohort 1A)**.

Participants who were randomized to receive placebo to match GS-6207 will receive oral GS-6207 and initiate their OBR on Day 15 **(Cohort 1B)**. They will receive SC GS-6207 at Day 1 SC (14 days after the first dose of oral GS-6207) while continuing their OBR.

After the Day 1 SC visit, all Cohort 1 participants will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52 (study visits Week X identified by the number of weeks that have elapsed since the Day 1 SC visit).

Cohort 2 (n 64)

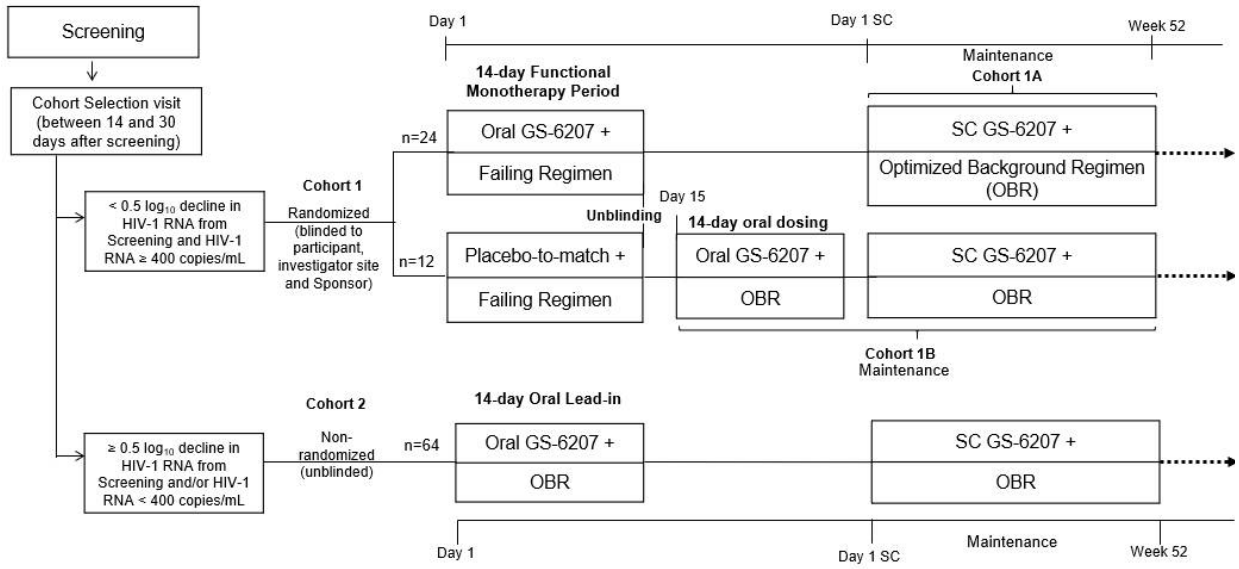
Oral Lead-in Period

Participants will be enrolled into Cohort 2 if Cohort 1 is fully enrolled or if they do not meet the criteria for randomization in Cohort 1 (eg, they had ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and/or HIV-1 RNA < 400 copies/mL at the Cohort Selection visit). Participants will be enrolled in Cohort 2 to receive oral GS-6207 for 14 days. Participants will initiate an OBR on Day 1.

Maintenance Period

At Day 1 SC (14 days after the first dose of oral GS-6207), participants will receive SC GS-6207 and will continue their OBR. After the Day 1 SC visit, participants will continue with study visits at Weeks 4, 10, 16, 22, 26, 36 and 52 (study visits Week X identified by the number of weeks that have elapsed since the Day 1 SC visit).

Study Design Schema



3.3. Study Treatments

Approximately 100 PLWH who meet all eligibility criteria may be enrolled in this study to receive GS-6207.

Cohort 1:

Functional Monotherapy Period: Participant will receive oral GS-6207 600 mg, 600 mg, and 300 mg or placebo to match GS-6207 on Days 1, 2, and 8 respectively while continuing their failing regimen; GS-6207 oral tablets can be administered without regards to food.

After each participant completes the Functional Monotherapy period, their treatment assignment will be unblinded.

Maintenance Period: At Day 1 SC (14 days after the first dose of oral GS-6207), participants who were randomized to receive oral GS-6207 will receive SC GS-6207 927 mg and initiate an optimized background regimen (as prescribed by the Investigator) (**Cohort 1A**). Participants will continue to receive SC GS-6207 927 mg once every 6 months (26 weeks).

At Day 15, participants who were randomized to receive placebo to match GS-6207 will receive oral GS-6207 600 mg and initiate an optimized background regimen (as prescribed by the Investigator). Participants will receive oral GS-6207 600 mg and 300 mg at Day 16 and Day 22 respectively. At Day 1 SC (14 days after the first dose of oral GS-6207), participants will receive SC GS-6207 927 mg while continuing their optimized background regimen (**Cohort 1B**). Participants will continue to receive SC GS-6207 927 mg once every 6 months (26 weeks).

Cohort 2:

Oral Lead-in Period:

At Day 1, participants will receive oral GS-6207 600 mg and initiate an optimized background regimen (as prescribed by the Investigator). Participants will receive oral GS-6207 600 mg and 300 mg at Day 2 and Day 8, respectively, while continuing their optimized background regimen; GS-6207 oral tablets can be administered without regards to food.

Maintenance Period:

At Day 1 SC, participants will receive SC GS-6207 927 mg while continuing their optimized background regimen. Participants will continue to receive SC GS-6207 927 mg once every 6 months (26 weeks).

3.4. Duration of Treatment

Participants will be treated for at least 54 weeks. Following completion of the Functional Monotherapy Period (Cohort 1) or the oral lead-in period (Cohort 2), participants will continue with study visits at Day 1 SC, Weeks 4, 10, 16, 22, 26, 36 and 52.

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Participants willing to continue the study beyond Week 52 visit will receive SC GS-6207 every 6 months (26 weeks) starting at Week 52 visit, while continuing their OBR, until the product becomes accessible to participants through an access program or until Gilead Sciences elects to discontinue the study in the country. Participants who decide not to receive SC GS-6207 at Week 52 and not to continue the study will complete the study at Week 52 visit. Participants who decides to discontinue SC GS-6207 early and do not wish to continue to attend study visits through Week 52 visit or next scheduled SC dosing visit will return to the clinic for 30-Day, 90-Day and 180-Day Follow Up visits after Early Termination Visit.. The 180-Day Follow Up may be conducted via a phone call per the investigator's discretion.

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4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 100 participants may be enrolled in this study.

36 participants will be enrolled in Cohort 1, and up to 64 may participants may be enrolled in Cohort 2.

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 (participants ≥ 18 years of age) and assent (participants ≥ 12 and < 18 years of age) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, parent or legal guardian willing and able to provide written informed consent prior to performing study procedures as required by local law

2) Adult aged ≥ 18 years (at all sites) or adolescent aged ≥ 12 and weighing ≥ 35 kg (at sites in North America and Dominican Republic)

3) Are receiving a stable failing ARV regimen for > 8 weeks before Screening and willing to continue the regimen until Day 1. Participants in Cohort 1 must also be willing to continue the failing regimen until completing the Functional Monotherapy Period (Day 1 to Day 14)

4) Have HIV-1 RNA ≥ 400 copies/mL at Screening

5) Have screening or available historical HIV resistance reports showing resistance to ≥ 2 antiretroviral medications from each of ≥ 3 of the 4 main classes of antiretroviral medications (NRTI, NNRTI, PI, INSTI). Resistance to FTC or 3TC associated with the presence of the M184V/I RT mutation cannot be used for the purpose of determining this eligibility criterion

6) Have ≤ 2 fully active ARV remaining from the 4 main classes that can be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant. Refer to Table 5-2 for list of disallowed ARVs

7) Able and willing to receive an optimized background regimen together with GS-6207. Participants with an OBR without a fully active agent may be enrolled if the investigator considers that there is a favorable risk-benefit ratio for the participant. With prior approval from Gilead Sciences, components of the OBR may be investigational (ie, not-yet-approved)

8) A negative serum pregnancy test is required for all women at Screening

9) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4.

10) Lactating women must agree to discontinue nursing before administration of GS-6207

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 the 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 visit

5) Untreated or newly treated (< 3 months prior to screening) Hepatitis B Virus (HBV) infection. Participants may be enrolled regardless of the HBV serology criteria below if they are receiving treatment with anti-HBV activity and plan to continue the treatment during the study. Hepatitis B infection is defined as screening results showing either or both of:

   a. Positive HBV surface antigen

   b. Positive HBV core antibody and negative HBV surface antibody. Participants may be enrolled with these findings if they have HBV DNA <LLOQ.

6) Hepatitis C virus (HCV) antibody positive and HCV RNA > LLOQ

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

8) Treatment within three 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 5-2 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 (GFR) ≤ 50 mL/min using Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age for creatinine clearance

    b. 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 IMP, 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, Enrollment, Blinding, and Treatment Codes Access

5.1.1. Randomization and Enrollment

Participants will be assigned a screening number using the Interactive Web Response System (IWRS) on the day of the Screening visit. Once eligibility has been confirmed and availability of OBR is confirmed, participants will be enrolled to either of the two cohorts as following:

- Cohort 1: Randomized in a 2:1 ratio to receive oral GS-6207 or placebo to match oral GS-6207 for 14 days starting on Day 1, while they continue their existing regimen

  OR

- Cohort 2: Enrolled to receive oral GS-6207 together with an OBR

Randomization or enrollment may occur approximately three days prior to Day 1 visit.

Each eligible participant will be assigned a unique participant number using IWRS. Once a participant number has been assigned, it will not be reassigned to another participant.

5.1.2. Blinding

During the Functional Monotherapy Period in Cohort 1, the investigational site(s), participants, and Gilead Sciences will remain blinded to treatment assignment and HIV-1 RNA results at Days 2 and 8. As each participant completes the Functional Monotherapy Period, their treatment assignment will be unblinded by investigational site using IWRS to determine their treatment regimen in the Maintenance Period. To mitigate the risks of inadvertently releasing the treatment information to participants who are still receiving functional monotherapy, Gilead staff will not receive the treatment codes from IWRS until all participants in Cohort 1 have completed the Functional Monotherapy Period. In the situation when Gilead staff is able to identify possible treatment assignment of participants still on blinded treatment, based on treatment information (eg, randomization block) from individual participants that have already been unblinded, they will maintain the confidentiality of the unblinded information, and will not communicate the information to blinded sites as specified in Gilead Standard Operating Procedures (SOPs).

Furthermore, specified personnel may be unblinded based on their study role. CCI [redacted] Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS for purposes of study drug inventory management will remain unblinded. Individuals in Gilead Global Patient Safety (GLPS) (formerly known as Pharmacovigilance and Epidemiology [PVE]) responsible for safety signal detection, IND safety reporting, and/or expedited reporting of suspected unexpected

serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group-level summaries. External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded to support safety data review specified in Section 7.8 of the protocol. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or regulatory agency inspections.

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment directly from the IWRS system for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

All participants will be followed until study completion, unless consent to do so is specially withdrawn by the participant.

5.2. Description and Handling of GS-6207 (Lenacapavir) Injection, GS-6207 (Lenacapavir) Tablets and Placebo to Match GS-6207 (Lenacapavir) Tablets

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.

Placebo to match 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. Placebo to match GS-6207 tablets, 300 mg contain the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide, iron oxide red, iron oxide black, 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 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.

Placebo to match GS-6207 tablets, 300 mg are packaged in white, HDPE bottles. Each bottle contains 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.

Study drugs to be distributed to centers in the US, EU and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), the J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs) 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 tablets, 300 mg should be stored below 30°C (86°F). Storage conditions are specified on the label. Placebo to match GS-6207 tablets, 300 mg should be stored below 30°C (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 GS-6207

Oral GS-6207 and GS-6207 injection for SC administration will be provided by Gilead Sciences. Participants will be responsible for continuing their pre-existing regimen. The OBR will be prescribed by the Investigator, and the participant is responsible for obtaining the OBR prior to their Day 1 visit. Medications disallowed as components of the OBR for pharmacokinetic reasons are provided in Section 5.4. Investigators should confirm the availability of the OBR prior to randomizing or enrolling eligible participants in IWRS.

Oral GS-6207 or Placebo to Match GS-6207 will be administered on Days 1, 2, and 8. Participants who receive Placebo to Match GS-6207 on Days 1, 2, and 8 will receive oral GS-6207 on Day 15, 16, and 22. Oral GS-6207 will be administered without regard to food. Oral dosing is presented in Table 5-1.

Table 5-1. Oral Dosing of GS-6207 or Placebo to Match

Study Visits	Treatment
Days 1 or 15*	600 mg
Days 2 or 16*	600 mg
Days 8 or 22*	300 mg

* Days 15, 16 and 22 visits are applicable only to participants who receive placebo to match in the Functional Monotherapy Period at Days 1, 2, and 8.

GS-6207 927 mg injection, 309 mg/mL will be administered in the abdomen via SC injections on Day 1 SC, Weeks 26, 52, and every 6 months (26 weeks) thereafter. GS-6207 injections should be administered at different abdominal sites no more than 15 minutes apart when possible. Each SC GS-6207 dosing should occur within 26 to 28 weeks of the previous SC GS-6207 dosing.

All study drug administration will occur on-site and without regard to food.

If a participant is not dosed within the protocol visit windows, and the investigator believes that it is in their 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.

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

5.4. 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 suggests 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 in Table 5-2and 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 5-2. 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*	ATV, ATV/co**, ATV/r, EFV, ETV, NVP, TPV**	
Digoxin		Digoxin: Concomitant use of oral GS 6207 may result in increased levels; 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 (eg, silymarin), Chinese herb sho saiko to (or Xiao Shai Hu Tang)	
HMG CoA Reductase Inhibitors		Concentrations of 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
Systemic Corticosteroids	All agents, including dexamethasone	

* ATV, atazanavir; co, cobicistat; EFV, efavirenz; ETV, etravirine; NVP, nevirapine; r, ritonavir; TPV, tipranavir
** Not approved in Japan

Physicians should refer to the package insert for the OBR medications for guidance on concomitant medications.

Investigators should make every effort to maintain the initial OBR. However, if clinically indicated for efficacy, safety, or tolerability reasons, investigators may change the OBR after consulting with Gilead's medical monitor. The reason for any changes to the OBR will be documented in the participant's source documents and the eCRF.

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.

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.

5.5. Accountability for Investigational Medicinal Product

The investigator (or designee, eg, study center pharmacist) 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). 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

5.5.1. Investigational Medicinal Product Return or Disposal for GS-6207 and Placebo to Match GS-6207 Tablets

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for 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.

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 the Gilead or 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. Pre-treatment Assessments

6.2.1. Screening Assessments

Participants will be screened within 42 days prior to enrollment in the study. Each participant will be assigned a unique screening number using the IWRS.

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, available HIV-1 treatment history, substance (ie, illicit drug) use and prior medications within 30 days of the Screening visit
- Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the Investigator) including, vital signs, 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
- Select an OBR based on the screening and/or available historical HIV resistance reports.

  Availability of selected OBR must be confirmed prior to randomization/enrollment and participant must be able to initiate OBR as specified in the protocol

- Return to the clinic between 14 and 30 days after the Screening visit, for a Cohort Selection visit. HIV-1 RNA results from this visit will be used to determine whether eligible participants will participate in Cohort 1 or Cohort 2.

  Once enrollment in Cohort 1 is complete, Cohort Selection visit will not be required.

Participants meeting all the inclusion criteria and none of the exclusion criteria will return to the clinic within 42 days after screening for a Day 1 visit. Participants will be instructed to continue their failing regimen.

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. Functional Monotherapy Period and Oral Lead-in Period Assessments

Cohort 1: Eligible participants will be randomized in Cohort 1 if they have a < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and HIV-1 RNA ≥ 400 copies/mL at the Cohort Selection visit. Approximately three days prior to the Day 1 visit, Investigator or designee may randomize the participant to receive oral GS-6207 or placebo to match GS-6207 and obtain a participant number using IWRS. Cohort 1 participants will have a Functional Monotherapy Period. Participants will continue to receive their failing regimen during this period.

Cohort 2: Eligible participants will be enrolled in Cohort 2 if Cohort 1 is fully enrolled or if they do not meet the criteria for randomization in Cohort 1 (eg, they had a ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the Screening visit and/or HIV-1 RNA < 400 copies/mL at the Cohort Selection visit). Approximately three days prior to the Day 1 visit, Investigator or designee may enroll the participant using IWRS and obtain a participant number. Cohort 2 participants will have an oral lead-in period and will initiate an OBR (as prescribed by the Investigator) on Day 1.

All participants will complete the following study visits: Days 1, 2, 5 (± 1 day) CCI [redacted] and 8. The following procedures are to be completed at the Day 1 visit, prior to study drug dosing and at Days 2, 5 (± 1 day) and 8, unless otherwise noted.

- Prior to completion of other study procedures, participants ≥ 18 years of age at the Day 1 visit will read the Patient Reported Outcomes, if available, by himself/herself and provide answers directly onto the questionnaires.

  Symptoms Distress Module, Short Form Health Survey (SF-36), EQ-5D-5L at Day 1

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the Investigator) (Day 1 only) or symptom directed physical examination as needed at Days 2 and 8
- Vital signs and body weight (except at Day 5)
- Obtain blood and urine samples collection as noted in Section 6.5
- After completion of study assessments, Cohort 1 participants will receive oral GS-6207 600 mg, 600 mg, and 300 mg or placebo to match on Days 1, 2, and 8 respectively.

  Cohort 1 participants will continue on their failing regimen
- After completion of study assessments, Cohort 2 participants will receive oral GS-6207 600 mg, 600 mg, and 300 mg on Days 1, 2, and 8 respectively.

  Cohort 2 participants will initiate an OBR (as prescribed by the Investigator) at Day 1. Participants will take last dose of their failing regimen prior to Day 1 visit
- All study drug dosing will occur at the study center without regard to food
- Document study drug administration
- After each participant completes the Functional Monotherapy Period, their treatment assignment will be unblinded

6.3.2. Maintenance Period Assessments

All participants will complete a Maintenance Period. The Gilead Medical Monitor should be consulted prior to administration of SC GS-6207 in the Maintenance Period if a participant was not administered all doses of oral GS-6207 during the Functional Monotherapy Period in Cohort 1 or the Oral Lead-in Period in Cohort 2.

All participants will complete the following study visits: Day 1 SC (14 days after the first dose of oral GS-6207), Weeks 4, 10, 16, 22, 26, 36 and 52. At the Week 52 visit, participants will be given an option to continue receive SC GS-6207 927 mg CCI [redacted] Participants willing to continue the study beyond Week 52 visit will receive SC GS-6207 every 6 months (26 weeks) starting at Week 52 visit, while continuing their OBR. Study visits Week X are identified by the number of weeks that have elapsed since the Day 1 SC visit when GS-6207 was first administered by injection.

Cohort 1B participants will complete the following study visits prior to receiving SC GS-6207: Days 15, 16, 19 (±1) CCI [redacted] and 22. They will receive oral GS-6207 600 mg, 600 mg, and 300 mg on Days 15, 16 and 22 respectively.

Week 4 visit through Week 52 visit are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 SC visit. Following the completion of Week 52 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.

The following procedures are to be completed at all visits unless otherwise noted.

- Participants ≥ 18 years of age at the Day 1 visit will read the Patient Reported Outcomes, if available, by himself/herself and provide answers directly onto the questionnaires.

  Participants will complete Symptoms Distress Module, Short Form Health Survey (SF-36), EQ-5D-5L at Weeks 4, 16, 26 and 52 (these questionnaires should be completed prior to the completion of other study procedures)

  Participants to complete the Numeric Pain Rating Scale at Day 1 SC, Weeks 26 and 52 (this questionnaire should be completed after the participant received their SC GS-6207 injections).

- Review of AEs and changes in concomitant medications

- Complete physical examination (Day 15 (Cohort 1B only), Day 1 SC, Weeks 26 and 52) (urogenital/anorectal examinations will be performed at the discretion of the Investigator) or symptom directed physical examination as needed (except at Days 5 and 19)

- Obtain vital signs and body weight (except at Days 5 and 19)

- Obtain blood and urine samples as noted in Section 6.5

- Cohort 1 participants who received oral GS-6207 during randomized phase will receive SC GS-6207 927 mg and initiate their OBR on Day 1 SC visit (14 days after the first dose of oral GS-6207) **(Cohort 1A).** Participants will continue to receive SC GS-6207 927 mg every 6 months (26 weeks) thereafter while continuing their OBR

- Cohort 1 participants who received placebo to match GS-6207 during randomized phase will receive oral GS-6207 600 mg and initiate their OBR on the Day 15 visit after completion of Day 15 assessments **(Cohort 1B).** Participants will receive oral GS-6207 600 mg and 300 mg on Days 16 and 22 respectively while continuing their OBR

- Cohort 1B participants will receive SC GS-6207 927 mg at the Day 1 SC visit while continuing on their OBR (14 days after the first dose of oral GS-6207). Participants will continue to receive SC GS-6207 927 mg every 6 months (26 weeks) thereafter while continuing their OBR

- Cohort 2 participants will receive SC GS-6207 927 mg at the Day 1 SC visit while continuing on their OBR (14 days after the first dose of oral GS-6207). Participants will continue to receive SC GS-6207 927 mg every 6 months (26 weeks) thereafter while continuing their OBR

- For all participants, study drug administration will occur at the study center without regard to food

- Provide injection site reaction assessment worksheet and instruct the participants to measure and report injection site reactions following the administration of the SC injections

- Document study drug administration

- Participants who meet the criteria for virologic failure will be managed according to the Management of Virologic Failure Section 6.7

6.4. Post-Treatment Assessments

6.4.1. Early Termination Visit Assessments

6.4.1.1 Early Termination visit after Day 1 and prior to Day 1 SC

If a participant discontinues oral GS-6207 or decides not to initiate SC GS-6207 at Day 1 SC, an Early Termination Visit should be performed within 72 hours of decision to discontinue the study drug. Participants in Cohort 1 will be asked to continue to attend study visits until completion of the functional monotherapy period. Participant will be required to complete the 90-Day Follow up Visit. Refer to Section 6.4.2

6.4.1.2 Early Termination visit after Day 1 SC and prior to Week 52

If a participant decides to discontinue SC GS-6207 prior to Week 52, 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 52 visit.

- If the participant decides to discontinue SC GS-6207 and agrees to continue to attend study visits through Week 52, no follow up visits are required.
- If the participant decides to discontinue SC GS-6207 and does not agree to continue to attend study visits through Week 52, 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.

6.4.1.3 Early Termination visit after Week 52

If a participant continues the study after completing the Week 52 visit, but discontinues SC **GS-6207** prior to study completion, an Early Termination Visit should be performed.

- If the participant discontinues SC GS-6207 and continues to attend study visits through their next SC dosing visit, all assessments, except SC dosing, will be performed at the last visit. No further follow up visits are required.

- If the participant discontinues SC GS-6207 and does not continue to attend 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 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 examinations will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- Obtain blood and urine samples as noted in Section 6.5
- Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility

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

The assessments below will be completed for participants who are required to complete 30-Day, 90-Day and/or 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. No follow up visits are required for those participants who do not receive SC GS-6207 at the Week 52 visit.

For 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, if there are any abnormal laboratory results indicating that there is a possible or probable causal relationship with the study drug, every attempt should be made to 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 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 visit 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 visit only)

- Chemistry profile: 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, uric acid (except at the Cohort Selection, Days 2, 5, 16 and 19 visits)

- Estimated GFR (except at the Cohort Selection, Days 2, 5, 16 and 19 visits) according to:

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

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

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

Schwartz Formula for participants < 18 years of age

Adolescent boys ≥ 12 years of age: 0.70 × L/ S_{Cr} (L is height in cm)

Adolescent girls ≥ 12 years of age: 0.55 × L/ S_{Cr} (L is height in cm)

- Hematology profile: complete blood count (CBC) with differential and platelet count (except at the Cohort Selection Visit, Days 2, 5, 16 and 19 visits)
- CD4+ cell count (except at the Cohort Selection Visit, Days 2, 5, 16 and 19 visits)
- Plasma HIV-1 RNA (except at Day 5 and 19)
- HIV-1 genotype and phenotype for PR, RT, IN, and capsid at Screening visit and any subsequent visit with virologic failure (described in Section 6.7).
- Hepatitis B virus (HBV) serologies (HBV surface antigen, HBV core antibody, HBV surface antibody) (Screening only)
- Hepatitis C virus (HCVAb) serology (Screening only)
- CCI [redacted]
- CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

6.5.3. 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 (except at Cohort Selection visit, Days 2, 5, 16 and 19 visits)
- Urine pregnancy test for women of childbearing potential (except at Screening, Cohort Selection Visit, Days 2, 5, 16 and 19 visits)

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

- Urine storage for possible additional clinical testing (except at Screening, Cohort Selection, Day 5, Day 19, and at 30, 90 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; participants may continue to receive study medication if the Investigator believes that there is medical benefit in doing so

- 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)

6.7. Management of Virologic Failure

Participants who experience suboptimal virologic response (SVR), virologic rebound (VR), or are viremic at their last visit, as defined below, will be considered to have virologic failure for the purposes of resistance analysis.

6.7.1. Suboptimal Virologic Response (SVR)

Suboptimal virology response is defined as:

- HIV-1 RNA ≥ 50 copies/mL **and** < 1 $\log_{10}$ HIV-1 RNA reduction from the start of oral GS-6207 (Day 1 for Cohort 1A and Cohort 2 participants, or Day 15 for Cohort 1B participants) at the Week 4 visit

Following the first instance of SVR at Week 4, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after first SVR visit) for confirmation of SVR. A plasma sample from either the first instance or the SVR confirmation visit will be tested for HIV-1 capsid genotypic and phenotypic resistance. In addition, if SVR is confirmed, a plasma sample from the SVR confirmation visit will be tested for HIV-1 PR, RT, and IN genotypic and phenotypic resistance.

6.7.2. Virologic Rebound (VR)

Virologic rebound is defined as:

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

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

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

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

6.7.3. Viremia at Last Visit

Participants with HIV-1 RNA ≥ 50 copies/mL at their last study visit (eg, not confirmable) will be analyzed for resistance (HIV-1 capsid, PR, RT, and IN resistance testing).

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

A 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 visit, 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 occurs after the participant first consents to participate in the study (i.e, signing the informed consent) and throughout the duration of the study, including the protocol-defined follow-up visit, must be reported on the applicable eCRFs and submitted to Gilead Global Patient Safety (GLPS) (formerly known as Pharmacovigilance and 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, 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 United States (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 investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study 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 (eg, 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. Before discontinuation of study drug for AEs or laboratory abnormalities, an assessment of the participants' medical situation including the potential for an alternative ARV regimen and the risk of resistance with subtherapeutic GS-6207 exposure should be made. Although routinely, participants with ≥ Grade 3 AEs or laboratory abnormalities that are considered related to the study drug should be discontinued, if alternative HIV therapies are not available, the participant may continue dosing with approval of the medical monitor following discussion with the investigator.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

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

For a Grade 3 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to study drug, consider withholding study drug 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 and is considered to be related to study drug, consider permanent discontinuation of study drug. The participant should be managed according to local practice.

Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation but requires discussion with the Gilead Medical Monitor.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

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

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK 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.

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.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

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 Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Section 6.4.2 for further information regarding protocol-defined follow-up period.

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, 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 Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead GLPS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead GLPS using the pregnancy outcome report form. If the pregnancy/outcome occurs after the study has been completed, including the protocol-defined follow-up period, but within 700 days of the last dose of SC GS-6207, the pregnancy/outcome should be reported directly to Gilead GLPS. 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 during the study, including the protocol-defined follow-up period, must also be reported and relevant information should be submitted to Gilead GLPS using the pregnancy and pregnancy outcome forms within 24 hours. If the end of 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 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, laboratory abnormality, and previously recognized adverse reaction across treatment groups based on predefined reporting thresholds, a safety monitoring committee will request review of 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 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 antiviral activity of GS-6207 administered as an add-on to a failing regimen (functional monotherapy) for PLWH with MDR as determined by the proportion of participants achieving at least 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period

The secondary objective of this study is:

- To evaluate the safety and efficacy of GS-6207 in combination with an optimized background regimen at Weeks 26 and 52

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8.1.2. Primary Endpoint

The proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of Functional Monotherapy Period.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

- The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 visits based on the US FDA-defined snapshot algorithm.

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses will be conducted for DMC meeting and for regulatory filings.

8.2.1.1. Dose Escalation Analysis

Not applicable.

8.2.1.2. Planned Internal Analysis

Interim analyses after the primary analysis (see Section 8.2.2) will be performed after all participants in Cohort 1 have completed their Week 52 visit and/or after all participants in Cohort 2 have completed their Week 26 visit or have prematurely discontinued the study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.2.1.3. DMC Analysis

There will be one planned DMC analysis of efficacy and safety. The DMC will convene after all participants in Cohort 1 have completed 14 days of assessment or discontinued the study drug in the Functional Monotherapy Period. Given that all participants have completed the Functional Monotherapy Period, treatment assignment will be unblinded for the DMC analysis.

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.

Gilead does not have a prior intent to ask the DMC to consider early termination of the study even if there is an early evidence of favorable efficacy. However, Gilead will stop further enrollment if 50% or more of the participants in the GS-6207 group fail in Cohort 1 to achieve at least 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period. The decision whether to continue with the study and the development of GS-6207 will be based on the magnitude of the HIV-1 RNA decline at the end of the Functional Monotherapy Period.

8.2.2. Primary Analysis

The primary analysis of the primary endpoint will be conducted after all participants in Cohort 1 have completed the Week 26 visit or have prematurely discontinued the 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. The data from this analysis will be used to support the GS-6207 regulatory filing for the indication in the heavily treatment experienced PLWH.

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 analysis is defined as full analysis set (FAS). Two FASs are defined for this study: one for the primary efficacy endpoint (referred to as "FAS for the Functional Monotherapy Period analysis") and the other for secondary efficacy endpoints (referred to as "FAS for the All GS-6207 analysis"). The FAS for the Functional Monotherapy Period includes all participants who are randomized and receive at least one dose of blinded study drug. In this analysis, participants will be grouped according to the treatment to which they are randomized. The FAS for the All GS-6207 analysis includes all participants who receive at least one dose of GS-6207.

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/enrolled 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 study will be included in the safety summaries.

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[redacted]

8.3.2. Data Handling Conventions

Logarithm (base 10) transformation will be applied to HIV-1 RNA levels for efficacy analysis.

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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 by cohort and treatment.

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

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

For Cohort 1, the Cochran-Mantel-Haenszel (CMH) test will be used to compare the 2 treatment groups for categorical data, and the 2-sided Wilcoxon rank sum test will be used to compare the treatment groups for continuous data. No statistical comparisons will be made for Cohort 2.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of participants in Cohort 1 achieving ≥ 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period. The primary analysis of the efficacy endpoint will be based on the FAS for the Functional Monotherapy Period.

The null hypothesis is that there is no difference in the proportion of participants achieving ≥ 0.5 $\log_{10}$ reduction from baseline at the end of the Functional Monotherapy Period (between the GS-6207 group and the Placebo group in Cohort 1); the alternative hypothesis is that there is a difference (GS-6207 Placebo) in the proportion of participants achieving ≥ 0.5 $\log_{10}$ reduction from baseline at the end of the Functional Monotherapy Period between the two treatment groups in Cohort 1. For participants with missing HIV-1 RNA values at the end of the Functional Monotherapy Period the value will be imputed using the last observation carried forward method. The difference in proportions between two treatment groups will be compared using an unconditional exact method using 2 invert 1-sided tests (Chan and Zhang 1999) with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the point estimate of treatment difference in proportions will be estimated and constructed using the above mentioned method.

8.5.2. Secondary Analyses

The proportion of participants in Cohort 1 with HIV-1 RNA < 50 copies/mL at Week 26 will be summarized using the US FDA-defined snapshot algorithm.

The analysis window at Week 26 is defined as from Study Day 184 to Study Day 232, inclusive, where Study Day is calculated from the first dose of GS-6207. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 26 analysis window

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

  Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 26 analysis window, or

  Who do not have on-treatment HIV-1 RNA data in the Week 26 analysis window and

  - Who discontinue study drug prior to or in the Week 26 analysis window due to lack of efficacy, or

  - Who discontinue study drug prior to or in the Week 26 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

- **No Virologic Data in the Week 26 analysis window:** this includes participants who do not have on-treatment HIV-1 RNA data in the Week 26 analysis window because of the following:

  Discontinuation of study drug prior to or in the Week 26 analysis window due to AE or death (regardless of whether the last available on-treatment HIV-1 RNA < 50 copies/mL or not) or,

  Discontinuation of study drug prior to or in the Week 26 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,

  Missing data during the window but on study drug.

The proportion of participants in Cohort 1 with HIV-1 RNA < 200 copies/mL at Week 26 will also be summarized using the US FDA-defined snapshot algorithm.

In addition, the proportion of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 52 will also be summarized using the US FDA-defined snapshot algorithm. The analysis window at Week 52 is defined as from Study Day 324 to Study Day 414, inclusive. The secondary endpoints will be based on the FAS for the All GS-6207 analysis. Analysis will be based on participants in Cohort 1 who receive at least one dose of SC GS-6207.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed will be summarized by cohort and treatment (according to the study drug received). All data collected 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 listed.

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. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug.

Summaries (number and percentage of participants) of treatment-emergent AEs (TEAEs) (by SOC, and PT) will be provided by treatment group.

8.6.3. Laboratory Evaluations

Selected laboratory data (using 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 the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline, will be summarized by cohort and treatment group. If baseline data are missing, any graded abnormality (eg, 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

The primary efficacy endpoint will be evaluated at the time when all participates in Cohort 1 have completed the Functional Monotherapy Period or discontinued the study drug. There will be no interim analyses before the analysis of the primary efficacy endpoint; therefore, no alpha level adjustment will be applied to the primary efficacy endpoint.

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8.9. Sample Size

A total of 36 participants in Cohort 1 will provide at least 90% power to detect a 60% difference in the proportion of participants achieving a ≥ 0.5 $\log_{10}$ reduction from baseline at Day 15 of the Functional Monotherapy Period between the treatment groups (GS-6207 in Cohort 1A and placebo in Cohort 1B).

In this sample size and power computation, it is assumed that 70% and 10% of participants achieve a ≥ 0.5 $\log_{10}$ reduction from baseline in HIV-1 RNA in the GS-6207 treatment group (Cohort 1A) and the placebo group (Cohort 1B), respectively (based on data from Trogarzo Phase 3 TMB-301 study {Emu 2018}), and the Fisher exact test is conducted at 2-sided significant level of 0.05.

A total sample size of 36 participants from Cohort 1A and 1B will provide reasonable assessment of safety through at least 24 weeks of GS-6207 treatment in heavily treatment experienced participants.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (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 adverse effects 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 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 participant 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, 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 investigator's brochure, this protocol, 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, eCRFs, 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 (eg, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

9.1.7. 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 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 eCRF Completion Guidelines (CCGs) provided by the Sponsor. After data entry, a study monitor

will perform source data verification (SDV) 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 in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, 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 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 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 authorities, 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.

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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 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living with HIV-1 Infection with Multidrug Resistance

GS-US-200-4625, Amendment 2 01 September 2020

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

Name (Printed)	Signature
PPD Clinical Research	

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Study Procedures Table

	Screening[a]	Cohort Selection[b]	Day 1[c]	Day 2	Day 5	Day 8	Day 15[d]	Day 16[d]	Day 19[d]	Day 22[d]	Day 1 SC	Weeks 4, 10, 16, 22, 26, 36	Week 52 and visits thereafter[e]	30, 90 and 180 Day Follow-Up[f]	Early Termination[g]
Written Informed Consent/Assent/Parental Consent	X														
Medical History	X														
Demographic Information	X														
Complete Physical Examination	X		X				X				X	X[h]	X[h]		X
Symptom Directed Physical Examination				X		X		X		X		X[h]	X[h]	X	
Vital Signs[i] (include weight)	X		X	X		X	X	X		X	X	X	X	X	X
12 lead ECG (supine)	X														
Height	X														
Hematology[j], Chemistry[k], Estimated GFR, Urinalysis[l], Urine Chemistry[l], CD4+ Cell Count	X		X			X	X			X	X	X	X	X	X
Urine Storage Sample			X	X		X	X	X		X	X	X	X		X
Serum Pregnancy Test[m]	X														
Serum FSH[n]	X														
Urine Pregnancy Test[m]			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

	Screening[a]	Cohort Selection[b]	Day 1[c]	Day 2	Day 5	Day 8	Day 15[d]	Day 16[d]	Day 19[d]	Day 22[d]	Day 1 SC	Weeks 4, 10, 16, 22, 26, 36	Week 52 and visits thereafter[e]	30, 90 and 180 Day Follow-Up[f]	Early Termination[g]
Plasma Storage Sample	X	X	X	X		X	X	X		X	X	X	X	X	X
CCI															
CCI															
CCI															
Oral GS 6207 Administration[t]			X	X		X	X	X		X					
Begin Optimized Background Regimen[u]			X				X				X				
SC GS 6207 Administration[v]											X	X	X		
Symptoms Distress Module, SF 36, EQ 5D 5L[w]			X									X	X		
Numeric Pain Scale[x]											X	X	X		
Injection Site Reaction Worksheet[x]											X	X	X		
Adverse Events/ Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening evaluations must be completed within 42 days prior to Day 1.
b Cohort Selection visit to be completed 14 to 30 days after the Screening visit until Cohort 1 is fully enrolled
c Day 1 tests and procedures must be completed prior to study drug administration
d Day 15, 16, 19 and 22 visits will be completed by Cohort 1B participants only
e At the Week 52 visit, CCI [redacted] Participants will receive SC GS 6207 every 6 months (26 weeks) starting at Week 52 visit, while continuing their OBR, until the product becomes accessible to participants through an access program or until Gilead Sciences elects to discontinue the study in the country.
f 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.

g Early Termination visit to be completed, if participant decides to discontinue study drug prior to completing Week 52 visit or prior to study completion. Investigators should 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

h Complete physical examination to be completed at Weeks 26 and 52, symptom directed physical examination to be completed at all other visits

i Vital signs blood pressure, pulse, respiration rate, and temperature, 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, uric acid (except at Cohort Selection, Days 2, 5, 16 and 19 visits)

l 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 (except at Cohort Selection, Days 2, 5, 16 and 19 visits)

m All women will have a serum test performed at Screening. Urine pregnancy test will be performed at all subsequent visits for women of child bearing potential (except at Days 2, 5, 16 and 19). Positive urine pregnancy tests will be confirmed with a serum test

n 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

[redacted]

q During the Maintenance Period, at all visits without SC GS 6207 injections: CCI [redacted]

r During the Maintenance Period, at all visits with SC GS 6207 injections: CCI [redacted]

[redacted]

t Cohort 1 participants will be administered oral GS 6207 or placebo to match GS 6207 at Days, 1, 2 and 8. Participants who receive placebo to match GS 6207 at Days 1, 2 and 8 will receive oral GS 6207 at Days 15, 16 and 22. Cohort 2 participants will be administered oral GS 6207 at Days 1, 2 and 8

u Cohort 1 participants will begin an OBR on Day 15 (Cohort 1B) or Day 1 SC (Cohort 1A). Cohort 2 participants will begin an OBR on Day 1. An OBR should be selected based on the screening and/or available historical HIV resistance reports.

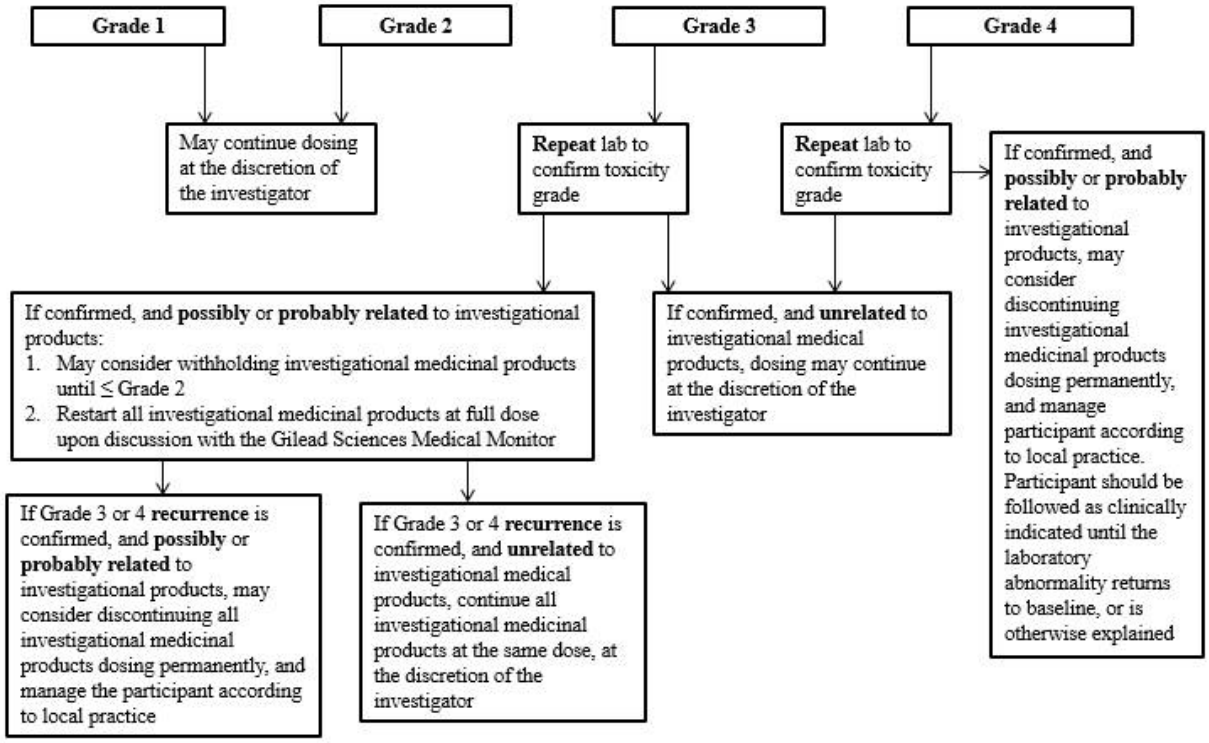
v All participants will be administered SC GS 6207 at Day 1 SC (14 days after the first dose of oral GS 6207) and will continue to receive SC GS 6207 every 6 months (26 weeks). Each SC GS 6207 dosing should occur within 26 and 28 weeks of the previous SC GS 6207 dosing.

w Participants ≥ 18 years of age at Day 1 visit will complete Symptoms Distress Module, SF 36, EQ 5D 5L at Day 1, Weeks 4, 16, 26 and 52, if available (before completing other study procedures).

x Participants ≥ 18 years of age at Day 1 visit will complete the Numeric Pain Rating Scale at Day 1 SC, Weeks 26 and 52 (after they receive SC GS 6207 injections)

y Provide injection site reaction assessment worksheet and instruct the participants to measure and report injection site reactions following the administration of the SC injections

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. For participants deemed by the investigator to have initiated puberty, no documentation of Tanner stage will be required.

Female born participants are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, female born participants < 54 years of age with amenorrhea of $\geq$ 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 purposes of this study, permanent sterilization is hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female born participant 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 assessment, 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.

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 Table (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 visit until 60 days after the last dose of oral study drug or 700 days following the last dose of SC 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 sterilization (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 (e.g. 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

* Not approved in Japan.

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 and within 700 days following the last dose of SC GS-6207. 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. Female born participants who become pregnant or who suspect that they are pregnant during the study should discontinue study drug immediately. 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:

- Completion of study visits which require on-site study drug administration:

  Oral and SC study drug administration must occur at the study site. Participants may be unable to return to the site, or the site may be unable to accept any participant visits. If a dosing visit is missed, the participant would not be able to complete dosing per protocol.

  Mitigation plan: Prior to initiation of study drug dosing, Investigator or designee should ensure Investigator or designee and participant availability to complete dosing visits from Day 1 through Day 1 SC visit. If oral or SC dosing (at Day 1 SC and subsequent) is not completed per protocol, sites should inform Sponsor immediately upon becoming aware of the issue and obtain Sponsor's input for participant's dosing management.

- Study drug shortage at the sites:

  Delayed or missed study drug shipment to the sites will cause a shortage of study drug at the sites.

  Mitigation plan: The Investigator or designee should closely monitor their study drug inventory. 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 principal investigator (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 AEs/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
- Remind participant to continue to administer other ARVs (failing regimen or optimized background regimen)

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 laboratory 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.

  Onsite 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.