CLINICAL SUBSTUDY-03 PROTOCOL

Study Title:	An Umbrella Phase 1b, Open-label, Multicohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1; Substudy-03: GS-6212
Plain Language Short Title:	Study of GS-6212 in Participants With HIV-1
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	162030
EU CT Number:	Not Applicable
ClinicalTrials.gov Identifier:	NCT05585307
Indication:	HIV-1 Infection
Protocol ID:	GS-US-544-5905-03
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 1: 18 August 2023
Amendment History:	Original: 08 June 2023 Amendment 1: 18 August 2023 High-level summaries of the history of amendment are provided in Appendix 11.4

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are not considered to be investigational new drug application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
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 $AUC_{last} + (C_{last}/\lambda_z)$
BVY	bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®)
$C_{av,ss}$	average steady state plasma concentration during multiple dose administration
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
conc	concentration
CT	computed tomography
C_{trough}	concentration at the end of the dosing interval
CV	coefficient of variation
D	Day
ECG	electrocardiogram
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IM	intramuscular
IND	investigational new drug
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
LA	long-acting
LDL	low-density lipoprotein
MAD	multiple ascending dose
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PWH	participant with HIV-1

RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SOC	standard of care
SRT	Safety Review Team
$t_{1/2}$	terminal elimination half-life
T_{max}	time (observed time point) of C_{max}
US, USA	United States, United States of America
WFI	water for injection

SUBSTUDY PROTOCOL SYNOPSIS

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

Study Title: An Umbrella Phase 1b, Open-label, Multicohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1; Substudy-03: GS-6212

Plain Language Short Title: Study of GS-6212 in Participants With HIV-1

Regulatory Agency Identifier Number(s):

IND Number: 162030
EU CT Number: Not applicable
ClinicalTrials.gov Identifier: NCT05585307

Study Sites Planned: See master protocol synopsis for study centers planned.

Objectives and Endpoints: See master protocol synopsis for objectives and endpoints.

Study Design:

This substudy is being conducted as part of an umbrella study as described in the master protocol.

Substudy-03 is an open-label, Phase 1b, multiple-dose, multicohort study to evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-6212 given as monotherapy in participants with HIV-1 (PWH) who are either treatment-naive or treatment-experienced but naive to integrase strand-transfer inhibitors (INSTIs) and have not received any antiretroviral (ARV) therapy (ART) within 12 weeks of screening, including medications received for pre-exposure prophylaxis or postexposure prophylaxis. Any current or prior receipt of long-acting (LA) parenteral ARVs, such as monoclonal antibodies targeting HIV-1, injectable cabotegravir, or injectable rilpivirine, is exclusionary.

After screening and meeting all eligibility criteria, study drug dosing will be initiated on Day 1 in the clinic for each participant (Figure 1). Participants will be required to return to the clinic for visits on Days 2, 3, 4, 7, 8, 9, 10, and 11 (primary endpoint assessment). Doses of GS-6212 will be administered orally at the clinic under observation by site staff on clinic visit days/times and at home by the participant on nonclinic visit days/times at approximately the same time each day. In cohorts where GS-6212 is administered more than once daily, in-clinic observation of dosing will be conducted for the morning dose only. Participants will record at-home dosing details in a dosing log.

After assessments on Day 11 or upon early termination (ET), participants will initiate a regimen of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; BVY) provided by the sponsor or an alternative standard of care (SOC) ART regimen selected by the investigator. If participants are switching to BVY, a sufficient supply will be given to provide coverage for the remainder of the study. Participants will be required to return to the clinic for a follow-up visit on Day 25.

Overnight fasting (≥ 6 hours prior to dosing) is required for laboratory and/or PK analyses on Days 1 and 11. On all other days (Days 2 through 10), the AM doses should be taken on an empty stomach.

This substudy will enroll up to 5 cohorts, with at least 6 participants in each cohort. Initial participants will be enrolled in Cohort 1, with dosing in subsequent cohorts proceeding after Safety Review Team (SRT) review of emerging data from Cohort 1 and available data from the Phase 1a single ascending dose (SAD)/multiple ascending dose (MAD) Study GS-US-469-6401.

Sequential enrollment in cohorts, and order of assignment to substudies, are described in Section 5.1.1 of the master protocol.

The sponsor may elect to hold dosing, stop/pause substudy enrollment, or stop the study (or substudy, or specific cohort) at any time based on review of preliminary safety, efficacy, and PK data (see master protocol Section 5.1.1). If deemed unnecessary, the sponsor may choose not to initiate 1 or more cohorts.

Number of Participants Planned: Up to 5 cohorts, each containing at least 6 participants, will be enrolled.

Study Population: See master protocol synopsis for the target population.

Diagnosis and Main Eligibility Criteria: See master protocol for diagnosis and main eligibility criteria. For inclusion in this substudy, participants must also be willing to initiate BVY provided by the sponsor, or an alternative SOC ART regimen selected by the investigator, on Day 11 or upon ET, and be willing and able to comply with meal requirements.

Test Product, Dose, and Mode of Administration:

In Cohort 1, a 100-mg dose of GS-6212 will be administered orally twice daily (ie, once every 12 hours ± 1 hour) on Days 1 through 10). The dose, dosing regimen, and meal requirements for administration of GS-6212 in Cohort 1 are provided in the table below. Subsequent cohort doses, dosing regimens, meal requirements (fasted or fed), and progression between cohorts will be adaptive. The maximum dose (to be administered each day at any given time) in subsequent cohorts will not exceed those indicated in the table below.

For participants who will be receiving GS-6212 once daily, study drug will be dispensed on Day 1. Bottles will be stored on site and administered in the clinic on Days 1 through 4. Participants will take doses at home on Days 5 and 6; doses on Days 7 through 10 will be administered in the clinic.

For participants who will be receiving GS-6212 twice daily, study drug bottles will be dispensed on Day 1. Participants will take the bottles home after the morning dose at the clinic and then bring the bottles back to the clinic for the next day's morning dose at the clinic for Days 1 through 4 and Days 7 through 10. For Days 5 and 6, participants will keep the bottles at home.

Doses of GS-6212 will be administered orally at the clinic under observation by site staff on clinic visit days/times and at home by the participant on nonclinic visit days/times at approximately the same time each day. In cohorts where GS-6212 is administered more than once daily, in-clinic observation of dosing will be conducted for the morning dose only. Participants will record at-home dosing details in a dosing log. In addition to the dosing log, site staff can remind the participant of evening dosing via phone call/text message, if feasible. The timing of all doses on Days 5 and 6 should be recorded in a dosing log.

Cohort	Treatment
Cohort 1	100 mg oral doses BID (ie, once every 12 hours ± 1 hour) on Days 1 through 10: - The first AM dose (on Day 1) should be taken following overnight fasting (≥ 6 hours). - All other AM doses (on Days 2 through 10) should be taken around the same time every morning on an empty stomach (fasting for ≥ 2 hours). - Each PM dose should be taken around the same time every evening with or without food. Participants are required to keep the pattern of study drug intake consistent throughout the 10 days of dosing as much as possible[a].
Cohort 2	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 3	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 4	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 5	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.

AM = before noon; BID = twice daily; PM = evening; QD = once daily

a For instance, if a participant takes their first PM dose on an empty stomach, then they should try and take the remainder of their PM doses on an empty stomach and vice versa.

If BVY is initiated after assessments on Day 11 or upon ET, it will be administered orally, once daily, without regard to food.

Reference Therapy, Dose, and Mode of Administration: Not applicable

Duration of Intervention: Up to 25 days

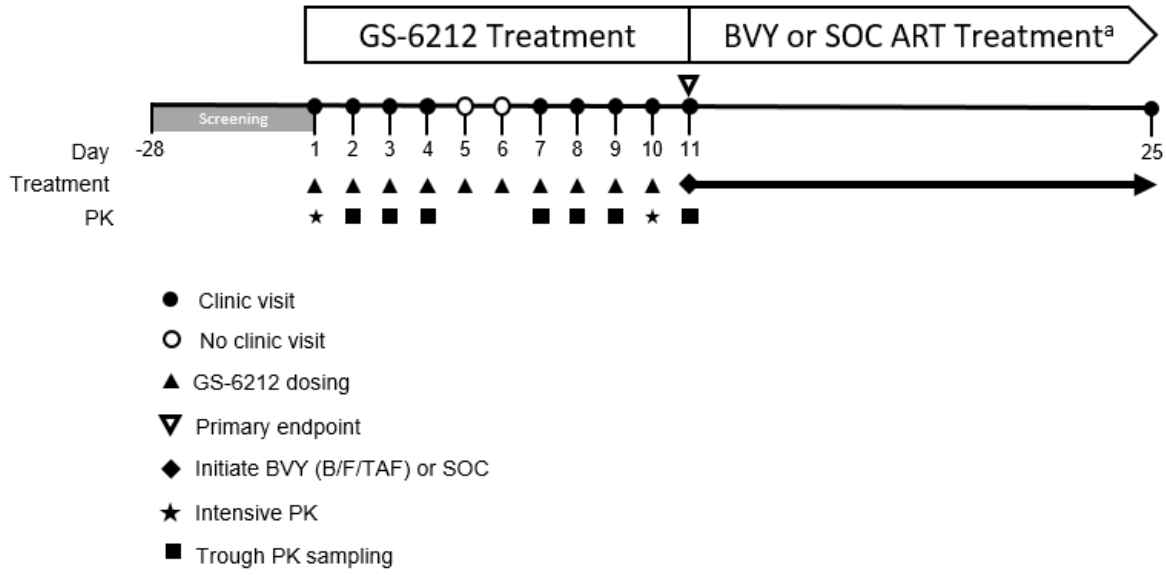
Study Procedures/Frequency: After screening and meeting all eligibility criteria, study drug dosing will be initiated on Day 1 in the clinic for each participant. Participants will be required to return to the clinic for visits on Days 2, 3, 4, 7, 8, 9, 10, and 11 (primary endpoint assessment). After assessments on Day 11 or upon ET, participants will initiate a regimen of BVY provided by the sponsor or an alternative SOC ART regimen selected by the investigator. Participants will be required to return to the clinic for a visit on Day 25.

The detailed schedule of procedures for Substudy-03 is provided in Table 1.

Statistical Methods: See master protocol synopsis for statistical methods.

SUBSTUDY-03 STUDY SCHEMA

Figure 1. Overview of Visits, Dosing, and Key Assessments for Substudy-03



ART = antiretroviral therapy; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®); PK = pharmacokinetic(s); SOC = standard of care

For Cohort 1, a dose of GS-6212 100 mg will be administered orally twice daily (ie, once every 12 hours ± 1 hour) on Days 1 through 10 (for further details on dosing and meal requirements, see Section 5.2.4). Subsequent cohort doses, dosing regimens, meal requirements (fasted or fed), and progression between cohorts will be adaptive and determined as summarized in Section 3.1.1.

a After assessments on Day 11 or upon early termination, participants will initiate a regimen of BVY provided by the sponsor or an alternative SOC ART regimen selected by the investigator. Participants who discontinue study drug before Day 11 should start this regimen at the time of discontinuation (see Section 6.4.1 of the master protocol).

STUDY PROCEDURES TABLE

Table 1. Substudy-03 Study Procedures Table

Study Procedure	Screening[a]	D1[b]	D2	D3	D4	D7	D8	D9	D10	D11[b]	D25	ET[c]
Visit Window											**±2D**	
Written informed consent	X											
Medical history and demography	X											
Complete physical examination	X	X									X	X
Symptom-driven physical examination[d]			X		X	X				X		
Height	X											
Weight	X	X		X		X				X	X	X
Vital signs[e]	X	X	X	X	X	X				X	X	X
HBV blood panel and HCV serology[f]	X											
CD4 cell count[f]	X	X								X	X	X
Plasma sample for HIV-1 genotyping/phenotyping[f,g]	X	X								X		
Plasma HIV-1 RNA[f]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[f]	X	X		X		X				X	X	X
Coagulation panel[f]	X	X				X				X	X	X
Chemistry[f]	X	X		X		X				X	X	X
Urinalysis[f]	X	X		X		X				X	X	X
Serum pregnancy test[f,h]	X											
Urine pregnancy test[f,h,i]		X									X	X
Serum FSH[f,j]	X											
12-Lead ECG	X	X				X				X	X	X
Intensive plasma PK[k]		X							X			
Single trough plasma PK[l]			X	X	X	X	X	X		X		X
Review AEs and concomitant medications[m]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug (GS-6212) dispensation[n]		X										
Study drug (GS-6212) dosing[o, p]		X	X	X	X	X	X	X	X			
BVY dispensation, as applicable										X		

Study Procedure	Screening[a]	D1[b]	D2	D3	D4	D7	D8	D9	D10	D11[b]	D25	ET[c]
Visit Window											**±2D**	
BVY or an alternative SOC administration										X[q]	→	

AE = adverse event; AM = before noon; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®); CD4 = clusters of differentiation 4; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus type 1; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event; SOC = standard of care

a Prospective participants should be screened no more than 28 days prior to administration of the first dose of study drug.
b Overnight fasting (≥ 6 hours prior to dosing) is required.
c ET assessments will be performed within 72 hours of prematurely discontinuing from the study or study drug, as applicable.
d Symptom-driven physical examinations will be performed as needed, based on reported signs and symptoms.
e Vital signs include blood pressure, heart rate, respiration rate, and body temperature. Participants should be sitting down for 5 minutes before vital sign measurements are obtained.
f See detailed list of laboratory assessments in Section 6.3.7 of the master protocol.
g Participants who meet the criteria for virologic failure at Day 11 will be tested for the potential development of resistance against all components of the treatment regimen, including the study drug. See Section 6.3.9.1.3 of the master protocol for management of virologic failure.
h Participants assigned female at birth and of childbearing potential only.
i A negative urine pregnancy test is required prior to study drug dosing on Day 1. Positive urine pregnancy tests will be confirmed with a serum test.
j A serum FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
k Intensive PK samples should be collected at these time points for all cohorts (relative to AM dosing): predose (≤ 30 minutes before dose), 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose (CCI [redacted]) on respective days of dosing (ie, Days 1 and 10). Please note that the 12-hour postdose sample (if collected) on Days 1 and 10 should be sampled prior to the administration of the PM dose, as applicable.
l Single trough PK sample should be drawn prior to AM drug dosing (as applicable) on the indicated dosing days (ie, Days 2, 3, 4, 7, 8, 9, and 11).
m From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.
n Study drug bottles of GS-6212 will be dispensed on Day 1 (see Section 5.2.4).
o For Cohort 1, a 100-mg dose of GS-6212 will be administered twice daily (ie, once every 12 hours ± 1 hour) on Days 1 through 10 (for further details on dosing and meal requirements, see Section 5.2.4). Subsequent cohort doses, dosing regimens, meal requirements (fasted or fed), and progression between cohorts will be adaptive and determined as summarized in Section 3.1.1.
p Participants will take their study drug doses at home on Days 5 and 6.
q After assessments on Day 11 or upon ET, participants will initiate a regimen of BVY provided by the sponsor or an alternative SOC ART regimen selected by the investigator. Participants who discontinue study drug before Day 11 should start this regimen at the time of discontinuation (see Section 6.4.1 of the master protocol).

1. INTRODUCTION

Substudy-03, conducted under the GS-US-544-5905 master protocol, will evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-6212 given as monotherapy in participants with HIV-1 (PWH) who are either treatment-naive or treatment-experienced but naive to the integrase strand-transfer inhibitor (INSTI) class, and have not received any antiretroviral (ARV) therapy (ART) within 12 weeks of screening (full population details provided in Section 4).

1.1. Rationale for Substudy-03

An overall rationale for the development of long-acting (LA) ARV agents is provided in the GS-US-544-5905 master protocol.

A rationale for the development of GS-6212 is provided below in Section 1.2.1.

1.2. Background on Study Interventions Used in Substudy-03

1.2.1. GS-6212

1.2.1.1. General Information

Integrase strand-transfer inhibitors have played an ever-growing role in disease treatment and are currently a key component of combination ARV therapies. There are currently 5 INSTIs approved for the treatment of HIV-1 infection. GS-6212 is a potent and selective INSTI with a favorable nonclinical pharmacology profile that supports its clinical development as a novel ARV agent for the treatment of HIV-1 infection, with the potential for injectable dosing once every 3 months. A broad spectrum of representative HIV-1 mutant variants resistant to nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, or capsid inhibitors remained fully sensitive to GS-6212, indicating that the compound should retain full antiviral potency against mutant variants from these ARV classes. Developing the novel INSTI GS-6212 to be combined with other LA ARVs would fulfill an unmet medical need for people with HIV-1 to provide safe and effective regimens that can be administered less frequently. For further information, refer to the current GS-6212 investigator's brochure (IB), including the following:

1) Nonclinical PK

2) Nonclinical pharmacodynamics

3) Nonclinical toxicology

1.2.1.2. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology studies are provided in the GS-6212 IB.

1.2.1.3. Clinical Studies of GS-6212

1.2.1.3.1. Study GS-US-469-6161

Study GS-US-469-6161 is an ongoing, Phase 1a, first-in-human, randomized, blinded (sponsor unblinded), placebo-controlled clinical study. In this study, healthy participants received or will receive single ascending doses (SAD) of GS-6212 using the following formulations and parenteral routes of administration: GS-6212 polyethylene glycol (PEG)/water for injection (WFI) suspension formulation (400 mg/mL) administered subcutaneously (SC, Part A), GS-6212 oil suspension formulation (350 mg/mL) administered SC (Part B), GS-6212 PEG/WFI suspension formulation (225 mg/mL) administered intramuscularly (IM, Part C), and GS-6212 PEG/WFI suspension formulation (400 mg/mL) administered IM (Part D). The study remains blinded, with follow-up ongoing.

Preliminary PK Summary

To characterize the PK of GS-6212 for injection, plasma samples will be collected up to Day 301 in each cohort. Interim PK analysis of samples until at least Day 7 postdose from cohorts that have been dosed thus far in Parts A, B, C, and D is ongoing.

Safety Summary

As of 12 May 2023, 75 participants have received either GS-6212 or placebo (randomized 4:1) by injection in Part A (n = 30; 200, 600, and 1200 mg), Part B (n = 20; 200 and 525 mg), Part C (n = 20; CCI and 225 mg) and Part D (n = 5; 200 mg). There have been no deaths, serious adverse events (SAEs), Grade 3 or higher adverse events (AEs), or discontinuations due to AEs reported. In a preliminary review of available safety data for 75 participants, as of 12 May 2023, the most common study drug (GS-6212 or placebo)–related AEs have been mild to moderate (Grade 1 and Grade 2) injection site reactions related to SC or IM administration and reported in 30% to 100% of participants across the different cohorts. Noninjection-site reaction study drug-related AEs were reported as follows: headache (n = 6), rash and pruritis (n = 1), and diarrhea (n = 1); all were Grade 1 and resolved without intervention. Other AEs included 1 participant who experienced presyncope related to micturition and 1 participant with asymptomatic atrial flutter at a Day 56 follow-up visit related to illicit drug use (cocaine). Both AEs resolved without intervention and were considered to be unrelated to GS-6212.

There were no clinically relevant changes from predose in values for hematology, clinical chemistry, urinalysis, or coagulation parameters in this preliminary review. Five participants had Grade 3 laboratory abnormalities; 3 participants had increased fasting low-density lipoprotein (LDL), 2 participants had increased fasting triglycerides, 1 participant had a decrease in CL_{cr} and a corresponding increase in serum creatinine from baseline but both values remained in the normal range. None of these Grade 3 laboratory abnormalities were considered clinically relevant. No Grade 4 laboratory abnormalities were reported.

No notable changes from predose were observed in vital signs (systolic and diastolic blood pressure, pulse, temperature, and weight).

1.2.1.3.2. Study GS-US-469-6401

Study GS-US-469-6401 is an ongoing, Phase 1a, randomized, blinded (sponsor unblinded), placebo-controlled clinical study. In this study, healthy participants received or will receive SAD or multiple ascending doses (MAD) of oral GS-6212. This study is being conducted in 2 parts (SAD Cohorts 1 through 4 and MAD Cohorts 5 through 7) that will include up to 7 cohorts. Additionally, Cohorts 2 and 3 will be conducted as a 2-period fixed-sequence design of the same single-dose levels of oral GS-6212 to assess any potential food effect.

Preliminary PK Summary

Preliminary GS-6212 plasma concentration-time profiles and associated PK parameters following administration of single oral doses of 100 mg (Cohort 1), CCI [redacted] under fasted and/or fed conditions, and CCI [redacted] under fasted conditions are presented in Figure 2, Figure 3, and Table 2 based on PK data available from Study GS-US-469-6401 as of 21 April 2023. Pharmacokinetic samples were collected for up to 72 hours postdose. Following oral administration of GS-6212 with or without food, GS-6212 was absorbed quickly with T_{max} observed from 1.0 to 4.0 hours postdose. The median oral GS-6212 $t_{1/2}$ ranged from approximately CCI [redacted] hours across the evaluated dose levels. All but 1 participant attained 5-fold of the protein-adjusted 95% effective concentration or inhibitory quotient (IQ) CCI [redacted] for GS-6212 by up to 2.0 hours postdose across all cohorts.

Over the dose range evaluated, the increase in AUC and C_{max} was less than dose-proportional in the fasted state. These less than dose-proportional increases in exposure suggest that oral GS-6212 exhibits nonlinearity in the dose-exposure relationship likely due to solubility-limited absorption.

Based on data from a limited sample size, GS-6212 exposure (as assessed by AUC_{inf} and C_{max}) following CCI [redacted] of a GS-6212 CCI [redacted] g dose with a high-fat meal was on average, approximately CCI [redacted] lower relative to GS-6212 CCI [redacted] dosed in fasted conditions. In comparison, CCI [redacted] of a GS-6212 CCI [redacted] dose with a high-fat meal led to, on average, an approximate CCI [redacted] increase in GS-6212 exposure relative to GS-6212 CCI [redacted] dosed in fasted conditions.

In line with the observed $t_{1/2}$ values, minimal accumulation in GS-6212 exposures was observed following 10 days of once-daily dosing in Cohorts 5 and 6.


CCI


CCI

CCI [redacted]

CCI

Cohort 1 (100 mg; Fasted)	Cohort 2 (CCI Fasted)	Cohort 2 (CCI ; Fed)	Cohort 3 (CCI ; Fasted)	Cohort 3 (CCI ; Fed)	Cohort 5 (CCI , Day 1; Fasted)	Cohort 5 (CCI QD × 10 days, Day 10; Fasted)	Cohort 6 (CCI , Day 1; Fasted)
1590 (17.2)	2790 (14.8)	1830 (37.8)	4720 (37.8)	5140 (41.2)	1430 (47.8)	1640 (32.3)	2900 (37.2)
2.00 (1.00, 2.75)	2.00 (1.25, 3.00)	3.00 (1.25, 4.00)	2.50 (2.00, 3.00)	4.00 (3.00, 4.00)	1.00 (0.625, 3.50)	2.00 (2.00, 3.75)	2.00 (0.625, 3.75)
8.32 (44.5)	26.1 (37.4)	25.2 (56.0)	120 (195)	366 (198)	12.7 (78.2)	15.5 (58.1)	17.0 (55.0)
1.60 (26.7)	3.94 (82.1)	4.06 (94.8)	2.87 (118)	5.63 (109)	12.7 (78.2)	1.73 (24.1)	17.0 (55.0)
48.0 (39.0, 48.0)	72.0 (54.0, 72.0)	72.0 (54.0, 72.0)	72.0 (72.0, 72.0)	72.0 (72.0, 72.0)	24.0 (24.0, 24.0)	72.0 (48.0, 72.0)	24.0 (24.0, 24.0)
6420 (28.2)	14,400 (19.1)	11,200 (38.4)	26,200 (32.9)	40,700 (48.9)	6590 (51.1)	7460 (38.6)	13,400 (40.3)
6500 (28.1)	14,800 (19.5)	11,600 (39.1)	27,000 (35.2)	42,900 (51.2)	6590 (51.1)	7650 (38.6)	13,400 (40.3)
6520 (28.1)	15,000 (20.5)	11,600 (39.2)	27,100 (35.3)	43,000 (51.2)	6660 (51.2)	—	13,500 (40.4)
0.259 (37.1)	1.05 (213)	0.440 (46.7)	0.201 (81.0)	0.183 (55.4)	1.02 (40.7)	—	0.597 (26.8)
6.42 (5.01, 10.1)	8.43 (6.68, 12.5)	9.33 (8.15, 14.8)	14.4 (12.2, 15.7)	11.4 (7.20, 13.2)	3.77 (3.33, 4.14)	8.84 (7.25, 10.5)	3.46 (3.28, 3.55)

CCI

h = hour; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; QD = once daily
PK parameters presented to 3 significant figures as mean (%CV) except $t_{1/2}$, T_{last}, and T_{max} which are presented as median (Q1, Q3).
Note: Analysis was conducted using nominal time points.

Safety Summary

As of 21 April 2023, 50 participants have received at least 1 dose of either GS-6212 or placebo in SAD Cohorts 1, 2, and 3 (100 mg, CCI) and MAD Cohorts 5 and 6 CCI and CCI for 10 days). Preliminary GS-6212 exposures for each cohort are found in Table 2 with the highest estimated exposure (preliminary AUC_{inf}) of 43,000 h•ng/mL in Cohort 3. In a preliminary blinded review of available safety data collected for 50 participants (SAD Cohorts 1, 2, and 3 and MAD Cohorts 5 and 6) as of 21 April 2023, there have been no deaths, SAEs, Grade 3 or higher AEs, or discontinuations due to AEs reported. One participant experienced a study drug (GS-6212 or placebo)–related treatment-emergent AE of Grade 1

headache, which resolved. One participant in Cohort 6 experienced treatment-emergent AEs of Grade 1 nausea and vomiting, along with headache and dizziness, on Days 1 and 2 respectively, which resolved without treatment and were judged by the investigator to be related to study drug (GS-6212 or placebo). This same participant experienced Grade 3 laboratory abnormalities for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on Day 13 which returned to baseline on retesting by Day 25; bilirubin levels and international normalized ratio remained normal, and acute viral hepatitis testing was negative.

Three participants had Grade 3 laboratory abnormalities; 1 participant had increased ALT and AST (discussed above) and a Grade 3 decrease in CL_{cr} from baseline with normal serum creatinine and normal CL_{cr}, 1 participant had increased LDL, which returned to baseline on retesting, and 1 participant had an increased triglyceride level that decreased on repeat testing. With the exception of the participant with elevated ALT and AST, no Grade 3 laboratory abnormalities were clinically significant or judged to be related to study drug. There were no other clinically relevant changes from predose in values for hematology, clinical chemistry, urinalysis, or coagulation parameters. No notable changes from predose were observed in vital signs (systolic and diastolic blood pressure, pulse, temperature, and weight).

1.3. Rationale for Dose Selection of GS-6212

Selection of the GS-6212 doses for this study takes into consideration the available safety, tolerability, and PK data for GS-6212 from the ongoing Phase 1a oral SAD and MAD study in healthy volunteers (Study GS-US-469-6401), as well as emerging preliminary safety and antiviral activity data in this substudy (as applicable).

As of 21 April 2023, 30 participants (24 active and 6 placebo) have received a CCI [redacted] of either GS-6212 CCI [redacted] or placebo in SAD Cohorts 1, 2, and 3, and 20 participants (16 active and 4 placebo) have received multiple oral doses of either GS-6212 CCI [redacted] or placebo in MAD Cohorts 5 and 6. In a preliminary blinded review of available safety data collected for 50 participants (Cohorts 1 through 3, and 5 and 6) as of 21 April 2023, GS-6212 dosed orally was generally safe and well-tolerated. A summary of preliminary safety data from Study GS-US-469-6401 is included in Section 1.2.

As of 21 April 2023, preliminary SAD PK data are available from Cohorts 1 through 3 at doses ranging from 100 CCI [redacted], and MAD PK data are available from Cohorts 5 and 6 at CCI [redacted] doses from Study GS-US-469-6401 (Figure 2, Figure 3, and Table 2). For the purposes of dose selection, both C_{trough} and the $C_{av,ss}$ were taken into consideration given that steady state is attained rapidly via the oral route in comparison to the SC/IM profiles that are expected to be relatively flatter with sustained exposures spanning over a wider interval. This may facilitate the extrapolation of the antiviral GS-6212 data from oral dosing to relevant clinical concentrations achieved with SC or IM formulations. Based on modeling and simulation using a preliminary population PK model, a 100-mg dose of GS-6212 administered orally twice daily (ie, once every 12 hours) from Days 1 through 10 will be used for Cohort 1 of this substudy. Modeling predicts that this regimen will result in a median GS-6212 C_{trough} at Day 11 that is approximately 4.7-fold above the IQ, with the median $C_{av,ss}$ predicted to be approximately 5.0-fold above the IQ5 (the estimated therapeutic threshold). The mean C_{max} of GS-6212 attained following a single oral

dose of 100 mg was approximately 1590 ng/mL (Table 2). Based on the available data, accumulation for GS-6212 exposures following twice daily dosing of 100 mg is expected to be minimal; the predicted median GS-6212 AUC and C_{max} for the proposed CCI [redacted] is approximately 3.0- to 3.5-fold lower than the highest observed AUC and C_{max} from the available preliminary analysis of Study GS-US-469-6401. Overall, GS-6212 exposures projected for Cohort 1 of the current study are well covered by the systemic levels of GS-6212 that have been shown to be safe in Study GS-US-469-6401 (see Section 1.2).

As part of this substudy, higher and/or lower GS-6212 doses/exposures relative to Cohort 1 will be evaluated in subsequent cohorts to target a wide range of IQ values that characterize the PK/pharmacodynamic relationship between GS-6212 PK and changes from baseline in HIV-1 viral load. Doses in Cohorts 2 to 5 (as applicable) will be determined by the Safety Review Team (SRT) based on cumulative safety, PK, and virologic data from Cohort 1, as well as relevant and available safety and PK data from the Phase 1a study (GS-US-469-6401). Doses selected for Cohorts 2 to 5 will be adaptive and will have projected GS-6212 exposures approximately at or below the observed exposures in the Phase 1a study.

1.4. Benefit-Risk Assessment for the Study

Potential risks to participants may include limited exposure to subtherapeutic concentrations of study drug. This could lead to the HIV-1 virus developing resistance to the study drug, and potentially to the study drug class, which could limit future treatment options. Strategies to mitigate this risk, and additional risk/benefit assessments applicable to Substudy-03 and GS-6212, are described in Section 1.4 of the master protocol.

2. OBJECTIVES AND ENDPOINTS

Objectives and endpoints are described in Section 2 of the master protocol.

3. STUDY DESIGN

3.1. Study Design Overview

This substudy is being conducted as part of an umbrella study as described in the master protocol.

Substudy-03 is an open-label, Phase 1b, multiple-dose, multicohort study to evaluate the safety, PK, and antiviral activity of GS-6212 given as monotherapy in PWH who are either treatment-naive or treatment-experienced but naive to INSTIs and have not received any ART within 12 weeks of screening, including medications received for pre-exposure prophylaxis or postexposure prophylaxis. Any current or prior receipt of LA parenteral ARVs, such as monoclonal antibodies targeting HIV-1, injectable cabotegravir, or injectable rilpivirine, is exclusionary.

After screening and meeting all eligibility criteria, study drug dosing will be initiated on Day 1 in the clinic for each participant (Figure 1). Participants will be required to return to the clinic for visits on Days 2, 3, 4, 7, 8, 9, 10, and 11 (primary endpoint assessment). Doses of GS-6212 will be administered orally at the clinic under observation by site staff on clinic visit days/times and at home by the participant on nonclinic visit days/times at approximately the same time each day. In cohorts where GS-6212 is administered more than once daily, in-clinic observation of dosing will be conducted for the morning dose only. Participants will record at-home dosing details in a dosing log.

After assessments on Day 11 or upon early termination (ET), participants will initiate a regimen of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; BVY) provided by the sponsor or an alternative standard of care (SOC) ART regimen selected by the investigator. If participants are switching to BVY, a sufficient supply will be given to provide coverage for the remainder of the study. Participants will be required to return to the clinic for a follow-up visit on Day 25.

Overnight fasting (≥ 6 hours prior to dosing) is required for laboratory and/or PK analyses on Days 1 and 11 (see Section 5.3). On all other days (Days 2 through 10), the AM doses should be taken on an empty stomach (for additional details see Section 5.3).

The selection of doses and dosing regimens for GS-6212 is described in Section 3.1.1.

This substudy will enroll up to 5 cohorts, with at least 6 participants in each cohort. Initial participants will be enrolled in Cohort 1, with dosing in subsequent cohorts proceeding after SRT review of emerging data from Cohort 1 and available data from the Phase 1a SAD/MAD Study GS-US-469-6401, as described in Section 3.1.1.

Sequential enrollment in cohorts, and order of assignment to substudies, are described in Section 5.1.1 of the master protocol.

The sponsor may elect to hold dosing, stop/pause substudy enrollment, or stop the study (or substudy, or specific cohort) at any time based on review of preliminary safety, efficacy, and PK data (see master protocol Section 5.1.1). If deemed unnecessary, the sponsor may choose not to initiate 1 or more cohorts.

3.1.1. Dose Selection/Modification

Enrollment and dosing with GS-6212 will begin with Cohort 1. The dose and regimen of GS-6212 for Cohort 1 is defined in Section 5.2.4.

A summary of planned SRT reviews, dose decisions, and cohort progression applicable to this substudy is included in Section 3.1.1 of the master protocol.

3.2. Duration of Intervention

Participants will be under evaluation in this Substudy-03 for 25 days.

Participants will receive doses of GS-6212 from Days 1 through 10; dosage and frequency will be specified as described in Section 5.2.4. Participants will then initiate a BVY or alternative SOC regimen following study assessments on Day 11 or upon ET for the remainder of the study. Participants will be required to return to the clinic for a follow-up visit on Day 25.

3.3. Substudy-03–Specific Discontinuation Criteria

Criteria for early discontinuation for individual participants, each substudy, and each substudy cohort are described in Section 3.3 of the master protocol.

3.4. Definitions for Time of Primary Endpoint and End of Study

Definitions for the time of the primary endpoint and end of study for each substudy are described in Section 3.4 of the master protocol.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection for Substudy-03

In Substudy-03, up to 5 cohorts, each containing at least 6 participants, will be enrolled. Participant replacement is described in Section 4.1.1 of the master protocol.

4.2. Substudy-03–Specific Inclusion Criteria

Inclusion criteria applicable to all substudies are provided in Section 4.2 of the master protocol. In addition to meeting the inclusion criteria in the master protocol, participants must also meet the following inclusion criteria to be eligible for participation in this substudy:

S03-1. Willing to initiate an SOC ART regimen on Day 11 or upon ET as stated in Section 4.2 of the master protocol. For this substudy, willing to initiate BVY provided by the sponsor or an alternative SOC ART regimen selected by the investigator on Day 11 or upon ET.

S03-2. Willing and able to comply with meal requirements.

4.3. Substudy-03–Specific Exclusion Criteria

Exclusion criteria applicable to all substudies are provided in Section 4.3 of the master protocol. In addition to not meeting any of the exclusion criteria in the master protocol, participants must not meet the following exclusion criterion to be eligible for participation in this substudy:

S03-1. Requirement for ongoing therapy with any prohibited medication listed in Section 5.4.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment and Treatment Code Access

Participant enrollment procedures are described in Section 5.1 of the master protocol.

5.2. Description and Handling of GS-6212 and BVY

BVY will be provided by the sponsor for use during the study, as applicable.

5.2.1. Formulation

GS-6212 tablets are available in strengths of CCI [redacted]. GS-6212 tablets CCI [redacted] GS-6212 tablets CCI [redacted] GS-6212 tablets CCI [redacted] The GS-6212 CCI [redacted] tablet formulation contains GS-6212, CCI [redacted] CCI [redacted]. The GS-6212 CCI [redacted] formulation contains GS-6212, CCI [redacted]

BVY tablets (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg) are capsule-shaped, film-coated, purplish brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. Each tablet core contains 50 mg of bictegravir (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). In addition to the active ingredients, the BVY tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with iron oxide red, iron oxide black, PEG, polyvinyl alcohol, talc, and titanium dioxide. Additional details are provided in local prescribing information for BVY product.

5.2.2. Packaging and Labeling

GS-6212 tablets are packaged in white, high-density polyethylene bottles. Each bottle contains 30 tablets and a silica gel desiccant. Each bottle is enclosed with a white, continuous-thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner. GS-6212 CCI [redacted] bottle configurations contain polyester packaging material. GS-6212 CCI [redacted] bottle configuration does not contain polyester packaging material.

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

Study drug(s) to be distributed to study sites in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice-Annex 13 (Investigational Medicinal Products) for Common Technical Document, or Annex 6 for Clinical Trial Regulation, as applicable, and/or other local regulations.

5.2.3. Storage and Handling

GS-6212 tablets should be stored below 30 °C. BVY should be stored according to the storage conditions specified on the label.

GS-6212 and BVY should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of GS-6212 and BVY and proper identification, the drug product should not be stored in a container other than that in which it is supplied.

5.2.4. Dosage and Administration

In Cohort 1, a dose of GS-6212 100 mg will be administered orally twice daily (ie, once every 12 hours ± 1 hour) on Days 1 through 10. The dose, dosing regimen, and meal requirements for administration of GS-6212 in Cohort 1 are provided in Table 3. Subsequent cohort doses, dosing regimens, meal requirements (fasted or fed), and progression between cohorts will be adaptive, as described in Section 3.1.1. The maximum dose (to be administered each day at any given time) in subsequent cohorts will not exceed those indicated in Table 3.

For participants who will be receiving GS-6212 once daily, study drug will be dispensed on Day 1. Bottles will be stored on site and administered in the clinic on Days 1 through 4. Participants will take doses at home on Days 5 and 6; doses on Days 7 through 10 will be administered in the clinic.

For participants who will be receiving GS-6212 twice daily, study drug bottles will be dispensed on Day 1. Participants will take the bottles home after the morning dose at the clinic and then bring the bottles back to the clinic for the next day's morning dose at the clinic for Days 1 through 4 and Days 7 through 10. For Days 5 and 6, participants will keep the bottles at home.

Doses of GS-6212 will be administered orally at the clinic under observation by site staff on clinic visit days/times and at home by the participant on nonclinic visit days/times at approximately the same time each day. In cohorts where GS-6212 is administered more than once daily, in-clinic observation of dosing will be conducted for the morning dose only. Participants will record at-home dosing details in a dosing log. In addition to the dosing log, site staff can remind the participant of evening dosing via phone call/text message, if feasible. The timing of all doses on Days 5 and 6 should be recorded in a dosing log.

Table 3. GS-6212 Dosage by Cohort

Cohort	Treatment
Cohort 1	100 mg oral doses BID (ie, once every 12 hours ± 1 hour) on Days 1 through 10: - The first AM dose (on Day 1) should be taken following overnight fasting (≥ 6 hours). - All other AM doses (on Days 2 through 10) should be taken around the same time every morning on an empty stomach (fasting for ≥ 2 hours; see Section 5.3). - Each PM dose should be taken around the same time every evening with or without food. Participants are required to keep the pattern of study drug intake consistent throughout the 10 days of dosing as much as possible[a] (see Section 5.3).
Cohort 2	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 3	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 4	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.
Cohort 5	CCI [redacted] on Days 1 through 10; dosing intervals and meal requirements (fasted or fed) to be determined based on relevant and available data from earlier cohorts.

AM = before noon; BID = twice daily; PM = evening; QD = once daily

a For instance, if a participant takes their first PM dose on an empty stomach, then they should try and take the remainder of their PM doses on an empty stomach and vice versa.

If BVY is initiated after assessments on Day 11 or upon ET, it will be administered orally, once daily, without regard to food.

5.3. Fasting and Meals (GS-6212 Dosing)

Cohort 1:

All GS-6212 doses will be administered at approximately the same time on each day (morning/evening) with 240 mL of water.

AM dosing:

The first AM dose of the study drug (on Day 1) should be administered following an overnight fast (no food or drinks, except water) for at least 6 hours. Participants should continue to fast until after collection of the 2-hour intensive PK sample, relative to time of dosing on Day 1. Additionally, participants will be restricted from water consumption 1 hour before and until 1 hour after dosing, except for the 240 mL given with the study drug on Day 1.

On all other days (ie, Days 2 through 10), participants should take the study drug on an empty stomach (no food or drinks except water, for at least 2 hours) and continue to fast until 1-hour postdose.

PM dosing:

Study drug should be taken every evening on an empty stomach (no food or drinks, except water, for at least 2 hours and continue to fast until 1-hour postdose) or with food. Additionally, overnight fasting (no food or drinks, except water) for at least 6 hours, is required for safety assessments on Day 11.

Participants are required to keep the pattern of study drug intake consistent throughout the 10 days of dosing as much as possible (for instance, if a participant takes their first PM dose on an empty stomach, then they should try and take the remainder of their PM doses on an empty stomach and vice versa).

Note: Fasting and meal requirements for the subsequent cohorts will be confirmed following availability of data from Cohort 1, and relevant and available data from the Phase 1a SAD/MAD Study GS-US-469-6401.

5.4. Prior and Concomitant Medications

See Section 5.3 of the master protocol for information on prior or concomitant medication rules applicable to this substudy, including restricted medications through Day 11. The investigator should reach out to the sponsor for guidance prior to the use of any concomitant medication from Day 1 through the end of study.

From Day 11 (following administration of BVY or an alternative SOC) through the last visit, the investigator should follow the local prescribing information for BVY or other ART taken as SOC (as applicable) by an individual participant.

5.5. Accountability for Study Drug Supplies: Study Drug and SOC ART Provided by the Sponsor (BVY)

Guidance related to accountability, return, and disposal of study drug supplies (study drug [GS-6212 for this substudy] and SOC ART provided by the sponsor [BVY for this substudy]) is provided in Section 5.4 of the master protocol.

6. STUDY PROCEDURES

Study procedures applicable to all substudies are listed in Section 6 of the master protocol. Study procedures specific to Substudy-03 are listed in the sections below. The time points for study procedures are specified in Table 1. Substudy-specific informed consent forms will be required for Substudy-03.

6.1. Instructions for Study Procedures

6.1.1. Pharmacokinetics

Blood samples will be collected to determine GS-6212 PK (and metabolites, if appropriate) in plasma as indicated in Table 1.

CCI [redacted]

6.1.2. Suboptimal Virologic Response

Management of suboptimal virologic response is described in Section 6.3.9.1.3 of the master protocol.

6.1.2.1. Management of Virologic Rebound

Management of virologic rebound is described in Section 6.3.9.1.3 of the master protocol.

6.1.2.2. Resistance Analysis at Participant's Last Visit

Resistance analysis at a participant's last visit is described in Section 6.3.9.1.3 of the master protocol.

6.1.3. Poststudy Care

The investigators will counsel and refer the participants to long-term care, including a human immunodeficiency virus treatment facility, and any medication assistance programs. Please see Section 3.5 of the master protocol.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

Adverse events are specified in Section 7 of the master protocol. Information regarding toxicity management that is specific to GS-6212 is described below and included in Appendix 11.3. Pregnancy precautions, definition of childbearing potential, and contraceptive requirements specific to GS-6212 are included in Appendix 11.2.

7.1. Toxicity Management

All clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.3 and as outlined below.

- Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results. The study drug may be continued without dose interruption for a clinically insignificant Grade 3 or 4 laboratory abnormality (eg, creatine kinase elevation after strenuous exercise, triglyceride elevation that is nonfasting or can be medically managed). Recurrences of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

- Grade 3 or 4 AEs, if considered unrelated to study drug, may not require dose interruption; continuation of study drug is at the discretion of the investigator.

7.1.1. Grades 1 and 2 Laboratory Abnormalities or AEs

- Continue study drug dosing at the discretion of the investigator.

7.1.2. Grade 3 Laboratory Abnormalities or AEs

- For a Grade 3 clinically significant laboratory abnormality confirmed by repeat testing that is considered related to study drug, the study drug should be permanently discontinued, and the investigator should consult the medical monitor and manage as clinically indicated. BVY or an alternative SOC should be initiated if clinically appropriate.

- For a Grade 3 AE considered to be related to the study drug, the study drug should be permanently discontinued, and the investigator should consult the medical monitor and manage as clinically indicated. BVY or an alternative SOC should be initiated if clinically appropriate.

7.1.3. Grade 4 Laboratory Abnormalities or AEs

- For a Grade 4 AE or clinically significant laboratory abnormality confirmed by repeat testing considered related to study drug, the study drug should be permanently discontinued, BVY or an alternative SOC should be initiated if clinically appropriate, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever comes 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.

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

Any questions regarding toxicity management should be directed to the sponsor's medical monitor.

8. STATISTICAL CONSIDERATIONS

Details of statistical methods will be provided in the statistical analysis plan for this substudy, including any deviations from the original statistical analyses planned. Statistical considerations for this substudy are described in Section 8 of the master protocol.

9. RESPONSIBILITIES

Details regarding responsibilities are specified in Section 9 of the master protocol.

10. REFERENCES

None.

11. APPENDICES

11.1. Investigator Signature Page

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

An Umbrella Phase 1b, Open-label, Multicohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1; Substudy-03: GS-6212

Amendment 1, 18 August 2023

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

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

11.2. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years of age with amenorrhea of at least 12 months may also be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

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

2) Contraception Requirements for Participants Assigned Female at Birth

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-6212 is contraindicated in pregnancy, as a malformative effect due to human teratogenicity/fetotoxicity is unknown. GS-6212 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, hormonal contraception is not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Refer to the latest version of the GS-6212 investigator's brochure for additional information.

Refer to the prescribing information for pregnancy and contraception information for the standard of care regimen.

b. Contraception Requirements for Participants Assigned Female at Birth of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the Day 1 visit before enrollment. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for participants assigned female at birth in this clinical study should start from the screening visit until the end of the protocol-defined follow-up period.

Participants assigned female at birth and 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 any of the following methods of birth control listed below:

- Nonhormonal intrauterine device
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

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.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Participants Assigned Male at Birth

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a partner assigned female at birth from exposure to the participant's seminal fluid and pose a potential risk to an embryo/fetus. A participant assigned male at birth with a partner assigned female at birth and of childbearing potential must use condoms during treatment and until the end of the protocol-defined follow-up period. If the partner assigned female at birth and of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Participants assigned male at birth must also refrain from sperm donation and cryopreservation of germ cells during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

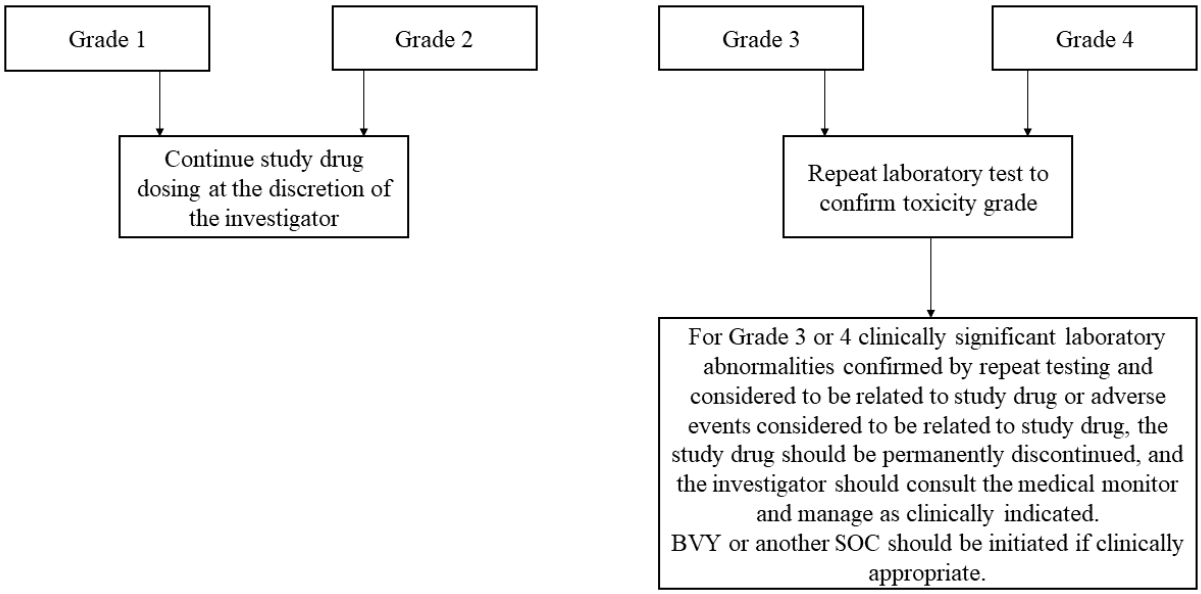
Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from the start of the study until the end of the protocol-defined follow-up period.

Participants assigned male at birth whose partner has become pregnant or suspects they are pregnant from start of study until the end of the protocol-defined follow-up period must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3 of the master protocol.

11.3. Management of Clinical and Laboratory Adverse Events



BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®); SOC = standard of care

11.4. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the original protocol to this amendment will be made available upon the publication of this protocol.

11.4.1. Amendment 1 (18 August 2023)

Rationale for Key Changes Included in Amendment 1	Affected Sections
A formulation for the new GS-6212 CCI has been added.	Sections 5.2.1 and 5.2.2
Minor changes such as the correction of typographic errors, grammar, or formatting.	Throughout, as needed.

11.5. Sponsor Signature Page

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

An Umbrella Phase 1b, Open-label, Multicohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1; Substudy-03: GS-6212

Amendment 1, 18 August 2023

APPROVAL OF CLINICAL STUDY PROTOCOL

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

PPD

Name (Printed)
Senior Director, Clinical Development

[See appended electronic signature]

Date

[See appended electronic signature]

Signature

Prot-GS-US-544-5905-03-amd-1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Project Team Leader eSigned	18-Aug-2023 22:26:00