CLINICAL SUBSTUDY-02 PROTOCOL

Study Title:	An Umbrella Phase 1b, Open-label, Multi-Cohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1 Substudy-02: GS-1720
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EudraCT Number:** **ClinicalTrials.gov Identifier:**	162030 Not applicable NCT05585307
Indication:	HIV-1 infection
Protocol ID:	GS-US-544-5905-02
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 27 February 2023 Amendment 1: 02 March 2023 Amendment 2: 05 May 2023 A high-level summary of amendment history is provided in Appendix 11.3.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312).

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
ART	antiretroviral therapy
ARV	antiretroviral
$AUC_{0\text{-}168h}$	area under the plasma drug concentration versus time curve from time zero to 168 hours postdose
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{inf}	area under the plasma drug concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
BVY	Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; coformulated)
C_{max}	maximum observed plasma drug concentration
EC_{95}	95% effective concentration
ET	early termination
FIH	first in human
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IB	investigator's brochure
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
LA	long acting
$paEC_{95}$	protein-adjusted 95% effective concentration
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PTM	placebo to match
PWH	people with HIV-1
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SOC	standard of care
SRT	safety review team
$t_{1/2}$	terminal elimination half-life
T_{max}	observed time point of C_{max}
US, USA	United States, United States of America

SUBSTUDY PROTOCOL SYNOPSIS

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

Study Title: An Umbrella Phase 1b, Open-label, Multi-Cohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1 Substudy-02: GS-1720

Regulatory Agency Identifier Numbers:

IND Number: 162030
EudraCT Number: Not Applicable
ClinicalTrials.gov Identifier: NCT05585307

Study Centers Planned

See master protocol synopsis for study centers planned.

Objectives and Endpoints:

See master protocol synopsis for objectives and endpoints.

Study Design: See master protocol synopsis for the overview of this substudy design.

Substudy-02 is an open-label, Phase 1b, single/multiple-dose, multicohort study to evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-1720 given as monotherapy in people with HIV-1 who are either treatment-naive or treatment-experienced but naive to the study drug class, and have not received any antiretroviral therapy (ART) within 12 weeks of screening, including medications received for preexposure prophylaxis or postexposure prophylaxis. Any current or prior receipt of long-acting parenteral antiretrovirals, such as monoclonal antibodies targeting HIV-1, injectable lenacapavir or 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. 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 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 follow-up visits on Days 25, 39, and 60.

Following study completion, the participant's care will transfer to a primary health care provider who will determine the participant's HIV long-term treatment plan. For participants

who complete the study, 6 and 12 months (± 1 month) after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV treatment regimen with date of change.

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 review of emerging data from Cohort 1.

The doses and dosing regimen for GS-1720 in each cohort will be selected based on a review of available PK, cumulative safety, and HIV-1 RNA data through the primary endpoint (Day 11) and/or relevant and available safety and PK data from the ongoing Phase 1a first-in-human study of GS-1720.

Number of Participants Planned: Up to 40 participants

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

Duration of Intervention: Approximately 60 days

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 on dosing 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 institute 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 follow-up visits on Days 25, 39, and 60. For participants who complete the study, 6 and 12 months (± 1 month) after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV treatment regimen with date of change.

The detailed schedule of procedures for Substudy-02 is provided in Table 1.

Test Product, Dose, and Mode of Administration:

Single or multiple doses of GS-1720 will be administered starting on Day 1. The dose, dose regimen, and meal requirements for administration of GS-1720 in Cohort 1 are provided below. Subsequent cohort dosing, dosing regimen (ie, single or multiple doses), meal requirements (fasted, or with a low-fat or high-fat meal), and progression between cohorts will be adaptive. Doses in subsequent cohorts will not exceed the doses indicated below.

Single or multiple doses of GS-1720 will be administered orally by site staff, at approximately the same time each day, with or without regard to food (as appropriate). The GS-1720 dose used in any cohort will not be higher than those previously evaluated in the Phase 1a study GS-US-615-6392.

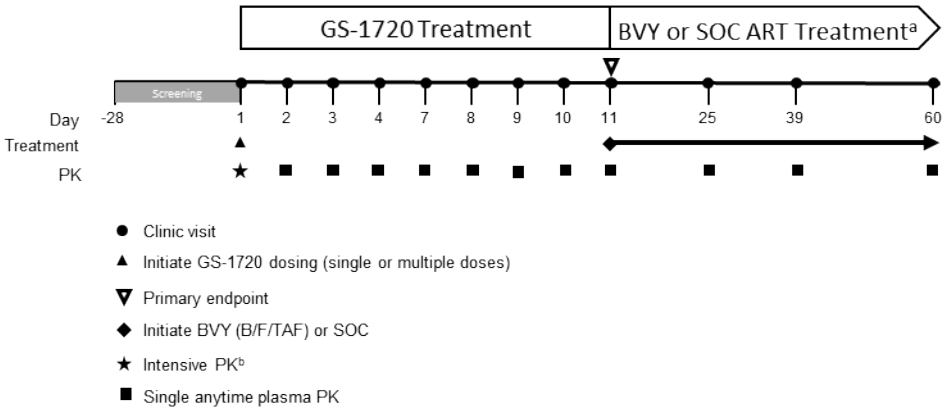
- Cohort 1: Single dose of GS-1720 450 mg administered on both Day 1 and Day 2 in the fasted condition
- Cohort 2: Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
- Cohort 3: Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
- Cohort 4: Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
- Cohort 5: Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)

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

Statistical Methods: See master protocol for statistical methods.

SUBSTUDY-02 STUDY SCHEMA

Figure 1. Overview of Visits, Dosing, and Key Assessments for Substudy-02



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

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.

b Additional intensive PK visits may be required for cohorts with more than 1 day of dosing of GS-1720.

For Cohort 1, a single 450-mg dose of GS-1720 will be administered on both Day 1 and Day 2 in the fasted condition. The doses, dosing regimen (single or multiple doses), and meal requirements for GS-1720 in each subsequent cohort will be selected based on a review of available PK, cumulative safety, and HIV-1 RNA data through the primary endpoint (Day 11), and/or relevant and available safety and PK data from the ongoing Phase 1a first-in-human study of GS-1720 (Section 3.1.1).

SUBSTUDY-02 STUDY PROCEDURES TABLE

Table 1. Substudy-02 Study Procedures Table

Study Procedure	Screening[a]	D1[b]	D2	D3[b]	D4	D7[b]	D8	D9	D10	D11[b]	D25[b]	D39[b]	D60[b]	ET[c]
Visit Window											**± 2D**	**± 2D**	**± 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	X	X
Vital signs[e]	X	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	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	X	X
Hematology[f]	X	X		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	X	X
Urinalysis[f]	X	X		X		X				X	X	X	X	X
Serum pregnancy test[f,h]	X													
Urine pregnancy test[f,h,i]		X									X		X	X
Serum FSH[f,j]	X													
12-Lead ECG	X	X				X				X			X	X
Intensive plasma PK[k,l]		X												

Single anytime plasma PK[m]			X	X	X	X	X	X	X	X	X	X	X	X
Review AEs and concomitant medications[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Initiate study drug (GS-1720) dosing[o]		X												
BVY dispensation										X				
BVY or SOC self-administration										X[p] →				
Investigator (or delegate) follow-up with primary health care provider	For participants who complete the study, 6 and 12 months (± 1 month) after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV treatment regimen with date of change.													

AE = adverse event; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); D = Day; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic(s); 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) 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 after Day 11 will be tested for the potential development of resistance against all components of the treatment regimen, including the evaluated compound. See Section 6.3.9.1.3 of the master protocol for management of virologic failure.
h Participants assigned female at birth 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 Serum FSH test is required for participants assigned female at birth and < 54 years old, not on hormonal contraception, and who have stopped menstruating for ≥ 12 months but do not have documentation of hormonal ovarian failure.
k Intensive PK samples should be collected at these time points for all cohorts: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose [redacted]) on respective days of dosing. Additional intensive PK visits may be required for cohorts with more than 1 day of dosing of GS-1720.
l For Cohort 1, intensive PK visits will be required for Day 1 and Day 2.
m Single anytime PK sampling will occur relative to study drug dosing on Day 1. Single anytime PK sampling will not be done if drug dosing and intensive PK sampling are performed on the same day.
n 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.
o For Cohort 1, a single 450-mg dose of GS-1720 will be administered on both Day 1 and Day 2 in the fasted condition (Section 5.2.4). Subsequent cohort dose, dosing regimen (ie, single or multiple dose), meal requirements (fasted or with a low-fat or high-fat meal), and progression between cohorts will be adaptive and determined as summarized in Section 3.1.1.
p BVY or SOC will be initiated on Day 11. Participants who discontinue study drug before Day 11 should start this regimen at the time of discontinuation (Section 6.4.1 of master protocol).

1. INTRODUCTION

Substudy-02, conducted under the GS-US-544-5905 master protocol, will evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-1720 given as monotherapy in people 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-02

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-1720 is provided below in Section 1.2.1.

1.2. Background on Study Interventions Used in Substudy-02

1.2.1. GS-1720

1.2.1.1. General Information

Integrase strand-transfer inhibitors play an ever-growing role in HIV-1 treatment, and are a key component of combination ARV therapies. Currently, there are 5 INSTIs approved for the treatment of HIV infection. As a class, INSTIs exhibit strong antiviral activity and excellent clinical tolerability. Notably, all approved oral INSTIs require once or twice daily dosing. Therefore, developing novel INSTIs with optimal oral LA PK that can be combined with other LA oral ARVs would fulfill an unmet medical need; ie, the availability of regimens that can be administered less frequently. GS-1720 is a novel potent and selective LA INSTI, engineered to have a long $t_{1/2}$ (projected to be approximately 240 hours), with a favorable nonclinical pharmacology profile that supports clinical development as a once weekly, oral ARV agent for the treatment of HIV infection.

For further information, refer to the current investigator's brochure (IB), including the following:

1. Nonclinical PK
2. Nonclinical pharmacodynamics (PD)
3. Nonclinical toxicology

1.2.1.2. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology studies are provided in the IB.

1.2.1.3. Clinical Studies of GS-1720

1.2.1.3.1. GS-US-615-6392

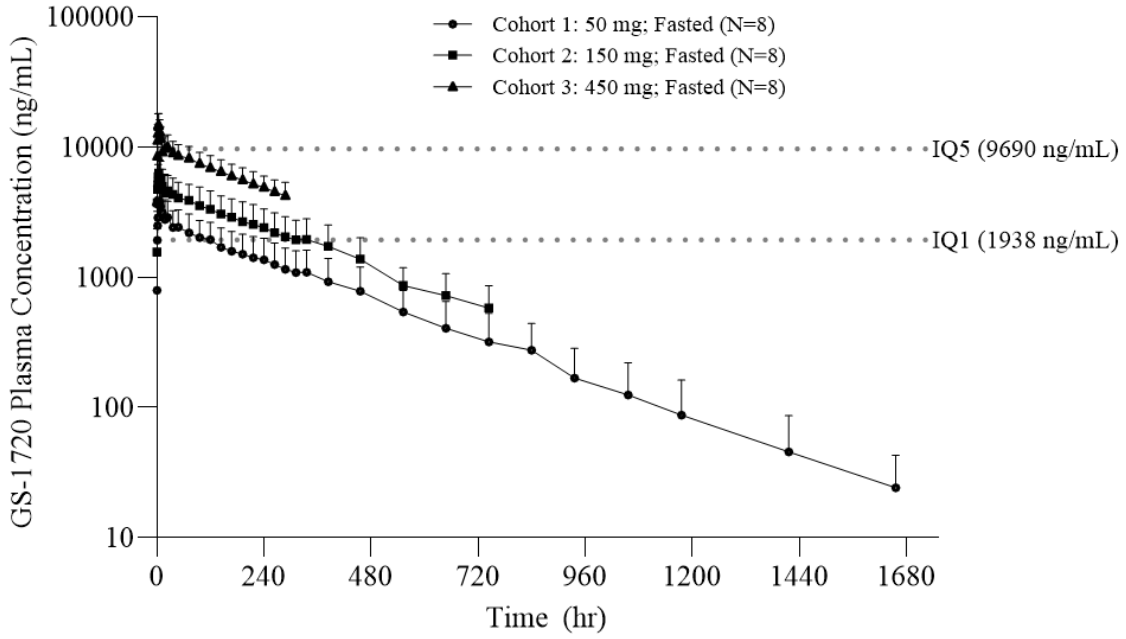
Study GS-US-615-6392 is an ongoing, first-in-human (FIH), Phase 1a study in healthy participants to evaluate the safety, tolerability, and PK of single and multiple ascending oral doses of GS-1720 up to 1350 mg. The study is planned to include up to 9 cohorts, each comprising at least 9 participants. Currently, participants have been enrolled in single ascending dose Cohorts 1 to 3 (n = 10/cohort) and received GS-1720 50-, 150-, and 450-mg doses (with Cohort 4 scheduled to receive GS-1720 1350 mg by 01 March 2023) (or placebo to match [PTM]), respectively, and multiple ascending dose Cohorts 5 and 6 (n = 9/cohort) and received, or are receiving, GS-1720 150- and 450-mg doses (or PTM), respectively, once weekly for 6 doses.

Preliminary PK Summary

Preliminary GS-1720 plasma concentration-time profiles and preliminary PK parameters after administration of single oral doses of 50 mg (Cohort 1), 150 mg (Cohort 2), and 450 mg (Cohort 3) GS-1720 in the fasted condition are presented in Figure 2 and Table 2, based on PK data available on 03 February 2023.

Median time to T_{max} of GS-1720 occurred between 3.5 and 4.0 hours. A 9-fold increase in dose (from 50 to 150 to 450 mg) resulted in a 3.5-fold higher C_{max} and 3.6-fold higher $AUC_{0\text{-}168h}$. Less than dose-proportional increases observed in C_{max} and $AUC_{0\text{-}168h}$ suggest that GS-1720 exhibits nonlinearity in dose-exposure relationship due to solubility-limited absorption.

Figure 2. GS-US-615-6392: Preliminary Mean (SD) GS-1720 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-1720 (N = 8 Per Cohort) in the Fasted Condition



IQ1, IQ5 = inhibitory quotient 1- or 5-fold higher than the protein-adjusted 95% effective concentration against wild-type HIV-1 virus ($paEC_{95}$: 1938 ng/mL)

Table 2. GS-US-615-6392: Preliminary PK Parameters of GS-1720 Following Single-Dose Administration of Oral GS-1720 (N = 8 Per Cohort) in the Fasted Condition

Parameter	Cohort 1 (50 mg, Fasted)	Cohort 2 (150 mg, Fasted)	Cohort 3 (450 mg, Fasted)
C_{max} (ng/mL)	4300 (28.3)	6860 (28.1)	15,000 (21.5)
T_{max} (h)	3.50 (2.25, 5.50)	4.00 (2.25, 5.50)	4.00 (3.00, 4.00)
$AUC_{0\text{-}168h}$ (h•ng/mL)	370,000 (35.5)	636,000 (33.0)	1,340,000 (22.2)
AUC_{inf} (h•ng/mL)	944,000 (46.1)	1,680,000 (41.1)	3,490,000 (29.4)
$\%AUC_{exp}$	0.74 (24.5)	8.17 (70.4)	40.3 (14.2)
$t_{1/2}$ (h) [days]	227 (206, 239) [9.47]	225 (206, 271) [9.37]	235 (218, 248) [9.77]

%CV = percentage coefficient of variation; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile.
PK parameters presented to 3 significant figures as mean (%CV), except for T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3) hours, with [median days] for $t_{1/2}$. Note: Preliminary analysis was conducted using nominal time points.

Safety Summary

In a preliminary blinded review of available safety data for 39 participants, as of 14 February 2023, no deaths, serious adverse events (SAEs), Grade 3 or higher adverse events (AEs), or discontinuations due to AEs were reported. Study drug (GS-1720 or PTM)-related AEs were reported for 3 participants; headache and vertigo were reported for 1 participant each in Cohort 3 (GS-1720 450 mg or PTM, single dose), and decreased appetite and paresthesia of the right foot were reported for 1 participant in Cohort 5 (GS-1720 150 mg or PTM, once weekly dose). None of these study drug-related AEs was serious.

There were no clinically relevant changes from predose in values for hematology, clinical chemistry, urinalysis, or coagulation parameters in this preliminary review. Three participants, all in Cohort 2 (GS-1720 150 mg or PTM, single dose), had Grade 3 laboratory abnormalities; 1 participant had glycosuria and a decrease in creatinine clearance, 1 participant had increased direct bilirubin (with no other signs or symptoms of hepatotoxicity), and 1 participant had an increase in creatine kinase. None of these Grade 3 laboratory abnormalities was 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).

1.3. Rationale for Dose Selection of Study Drug

Selection of GS-1720 doses for this study takes into consideration the available safety, tolerability, and PK data for GS-1720 from the ongoing FIH study with oral single and multiple ascending doses in healthy volunteers (Study GS-US-615-6392), as well as emerging preliminary safety and antiviral data in this substudy.

As of 14 February 2023, 30 participants (24 active and 6 placebo) had received a single oral dose of GS-1720 (50 to 450 mg) or PTM, and 9 participants (6 active and 3 placebo) had received multiple oral doses of GS-1720 (150 mg) or PTM. In a preliminary blinded review of available safety data from 39 participants, as of 14 February 2023, GS-1720 was generally well tolerated. No deaths, SAEs, Grade 3 or higher AEs, or discontinuations due to AEs were reported. Three participants had Grade 3 laboratory abnormalities, none of which was considered clinically relevant. No Grade 4 laboratory abnormalities were reported.

As of 17 February 2023, available preliminary PK data from Study GS-US-615-6392 showed less than dose-proportional PK of GS-1720 following single doses of 50, 150, and 450 mg (Figure 2 and Table 2). Based on modeling and simulation, a 450-mg dose of GS-1720 given on both Day 1 and Day 2 is expected to result in a GS-1720 plasma concentration at Day 11 (ie, 240 h from the first dose) that is approximately 5-fold the inhibitory quotient (IQ), defined as the in vitro-derived protein-adjusted 95% effective concentration against the wild-type HIV-1 virus ($paEC_{95}$: 1938 ng/mL), and is selected for evaluation in Cohort 1 of this substudy. GS-1720 exposures projected for Cohort 1 (450 mg on Day 1 and 450 mg on Day 2, taken approximately 24 h apart) are expected to be well covered by exposures in multiple ascending dose Cohort 6 in the FIH study. Preliminary clinical safety and PK data from Cohort 6, in which participants are

given a 450-mg dose of GS-1720 once weekly for 6 weeks (initial dosing completed on 23 February 2023), will be reviewed by the safety review team [SRT]. Higher and/or lower doses will be evaluated in subsequent cohorts to target a range of IQ values that characterize the PK-PD relationship between GS-1720 PK and changes from baseline in HIV-1 viral load. Doses in Cohorts 2 to 5 will be determined by the SRT based on cumulative safety, PK, and virologic data from Cohort 1, as well as safety and available PK data from the FIH study (Study GS-US-615-6392). Doses selected for Cohorts 2 to 5 will be adaptive and have projected exposures within the range of observed exposures in the FIH study.

1.4. Benefit-Risk Assessment for the Study

Potential risks to participants may include prolonged exposure (several weeks) to subtherapeutic concentrations of study drug. This could lead to the development of resistance to the study drug and, potentially, the study drug class, which could limit future treatment options. Strategies to mitigate this risk, and additional benefit-risk assessments applicable to Substudy-02 and GS-1720, 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-02 is an open-label, Phase 1b, single/multiple-dose, multicohort study to evaluate the safety, PK, and antiviral activity of GS-1720 given as monotherapy in PWH who are either treatment-naive or treatment-experienced but naive to the study drug class and have not received any ART within 12 weeks of screening, including medications received for preexposure prophylaxis or postexposure prophylaxis. Any current or prior receipt of LA parenteral ARVs, such as monoclonal antibodies targeting HIV-1, injectable lenacapavir or 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). 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 follow-up visits on Days 25, 39, and 60. Overnight fasting (≥ 6 hours) is required for laboratory analyses prior to visits on Days 1, 3, 7, 11, 25, 39, and 60.

Following study completion, the participant's care will transfer to a primary health care provider who will determine the participant's HIV long-term treatment plan. For participants who complete the study, 6 and 12 months (± 1 month) after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV treatment regimen with date of change.

The selection of doses and dosing regimens for GS-1720 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, 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).

3.1.1. Dose Selection/Modification

Enrollment and dosing with GS-1720 will begin with Cohort 1. The dose and regimen of GS-1720 for Cohort 1 is defined in Section 5.2.4.

A summary of 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 Substudy-02 for 60 days.

Participants will receive single or multiple doses of GS-1720, starting on Day 1. Participants will then initiate a BVY or alternative SOC regimen following study assessments on Day 11 for the remainder of the study. Participants will be required to return to the clinic for follow-up visits on Days 25, 39, and 60.

3.3. Substudy-02 Specific Discontinuation Criteria

Criteria for early discontinuation from the substudy for individual participants are described in Section 3.3.1 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-02

In Substudy-02, 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-02-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:

S02-1. Willing to initiate an SOC ART regimen on Day 11 or upon ET as stated in Section 4.2 in 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.

S02-2. Willing and able to comply with meal requirements on dosing days.

4.3. Substudy-02-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:

S02-1. Requirement for ongoing therapy with any prohibited medication listed in Section 5.3.

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-1720 and BVY

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

5.2.1. Formulation

GS-1720 tablets are available in strengths of 10, 50, and 250 mg. GS-1720 10- and 50-mg tablets are round, plain-faced, film-coated, beige tablets. GS-1720 250-mg tablets are capsule-shaped, plain-faced, film-coated, beige tablets. In addition to the active ingredient, GS-1720 tablets also contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide yellow, and ferrosoferric oxide.

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, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Additional details are provided in local prescribing information for BVY product.

5.2.2. Packaging and Labeling

GS-1720 tablets are packaged in white, high-density polyethylene bottles containing silica gel desiccant and polyester packing material. Each bottle is sealed with a white, continuous-thread, child-resistant, polypropylene screw cap with an induction-sealed, aluminum-faced liner.

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

Study drug to be distributed to centers in the United States (US) and other participating countries will be labeled to meet applicable requirements of the US Food and Drug Administration and/or other local regulations as applicable.

5.2.3. Storage and Handling

GS-1720 tablets should be stored below 30 °C. BVY should be stored according to the storage conditions specified on the label.

GS-1720 and BVY should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of GS-1720 and BVY and proper identification, the drug products should not be stored in a container other than that in which they are supplied.

5.2.4. Dosage and Administration

Single or multiple doses of GS-1720 will be administered starting on Day 1. The dose, dosing regimen, and meal requirements for administration of GS-1720 in Cohort 1 are provided in Table 3. Subsequent cohort doses, dosing regimens (ie, single or multiple doses), meal requirements (fasted, or with a low-fat or high-fat meal), and progression between cohorts will be adaptive, as described in Section 3.1.1. Doses in subsequent cohorts will not exceed those indicated in Table 3.

Single or multiple doses of GS-1720 will be administered orally by site staff, at approximately the same time each day (in the case of multiple dose regimens), with or without regard to food (as appropriate). The GS-1720 dose used in any cohort will not be higher than those previously evaluated in the Phase 1a Study GS-US-615-6392.

A low-fat/moderate calorie breakfast (400-500 calories; 100-125 calories from fat) or a high-fat/high-calorie breakfast (800-1000 calories; 500-600 calories from fat) may be initiated 30 minutes prior to study drug administration. Participants may be administered GS-1720 at or within 5 minutes of participants consuming the meal.

Table 3. GS-1720 Dosage by Cohort

Cohort	Treatment
Cohort 1	A single dose of GS-1720 450 mg will be administered on both Day 1 and Day 2 in the fasted condition
Cohort 2	Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 3	Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 4	Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 5	Single or multiple doses of GS-1720 up to 1350 mg administered in the fasted condition or with food (low-fat or high-fat meal)

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. 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 11 through the end of the study.

From Day 11 through the last visit, the investigator should follow local prescribing information for BVY or other ART taken as SOC by an individual participant.

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

Guidance related to accountability, return, and disposal for study drug supplies (study drug [GS-1720 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 studies are listed in Section 6 of the master protocol. Study procedures specific to Substudy-02 are listed in the sections below. The time points for study procedures are specified in Table 1. A substudy-specific informed consent form will be required for Substudy-02.

6.1. Instructions for Study Procedures

6.1.1. Pharmacokinetics

Blood samples will be collected to determine GS-1720 PK (and metabolites, if appropriate) in plasma as indicated in Table 1.

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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. Investigator Follow-up With Primary Health Care Provider

For participants who complete the study, 6 and 12 months (± 1 month) after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV treatment regimen with date of change. At each time point, the investigator (or delegate) should make and document at least 3 attempts of contact over a period of 4 weeks.

These data are derived from secondary use data (previously collected for other purposes), therefore collection and submission of AEs are not required.

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-1720 is described below, and included in Appendix 11.2. Pregnancy precautions, definition of female of childbearing potential, and contraceptive requirements specific to GS-1720 are included in Appendix 11.1.

7.1. Toxicity Management

All clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.2 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 multiple-dose cohorts for a clinically insignificant Grade 3 or 4 laboratory abnormality (eg, creatine kinase elevation after strenuous exercise, or 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 clinical events, if considered unrelated to study drug, may not require dose interruption; continuation of study drug for multiple-dose cohorts is at the discretion of the investigator.

7.1.1. Grade 1 and 2 Laboratory Abnormalities or Clinical Events

- Continue study drug at the discretion of the investigator for multiple-dose cohorts, as applicable.

7.1.2. Grade 3 Laboratory Abnormalities or Clinical Events

- For a Grade 3 clinically significant laboratory abnormality confirmed by repeat testing that is considered related to study drug, the study drug should be withheld in multiple-dose cohorts and the medical monitor consulted.

7.1.3. Grade 4 Laboratory Abnormalities or Clinical Events

- For a Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing considered related to study drug, the study drug should be permanently discontinued in multiple-dose cohorts 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. 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 female participant 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-1720 is contraindicated in pregnancy as any malformative effect is unknown. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. GS-1720 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 investigator's brochure (IB) for additional information.

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

The inclusion of participants assigned female at birth 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 female participants 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 one 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

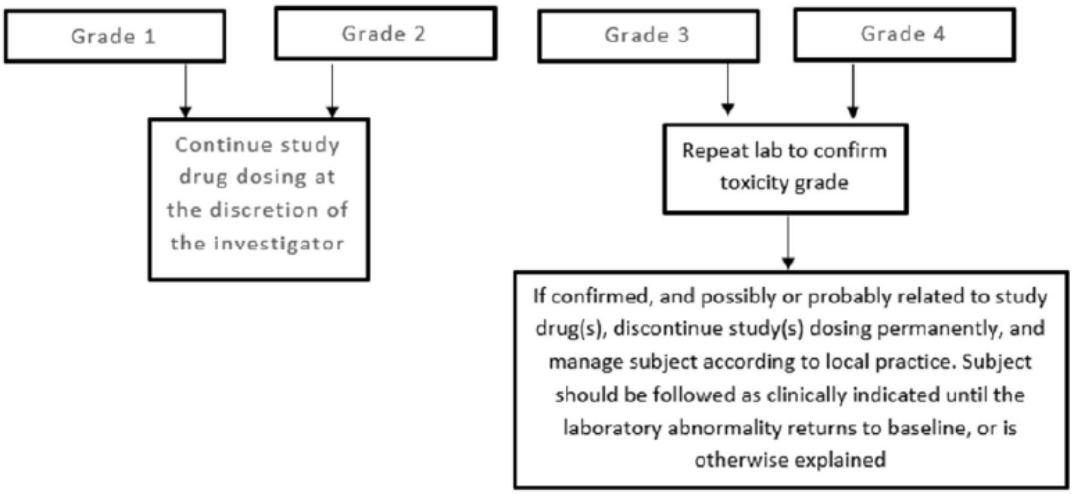
Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

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.

11.2. Management of Clinical and Laboratory Adverse Events



11.3. Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsections below (from most recent amendment to oldest), 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 protocol amendment 1 to this amendment will be made available upon the publication of this protocol.

11.3.1. Amendment 2 (05 May 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Per Food and Drug Administration (FDA) request, additional language included noting following study completion, the participant's care will transfer to a primary health care provider who will determine the participant's HIV long-term treatment plan. For those participants who complete the study, 6 and 12 months after enrollment the investigator (or delegate) will contact the participant's primary health care provider to request and record all available plasma HIV-1 RNA and resistance testing results and, if applicable, changes in HIV regimen with date of change.	Synopsis, Table 1, Sections 3.1 and 6.1.3
Minor changes included to correct typographic errors.	Throughout, as required

11.3.2. Amendment 1 (02 March 2023)

Rationale for Key Changes Included in Amendment 1	Affected Sections
References to the United States prescribing information for Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; BVY) removed as sites outside of the United States will be involved; replaced with reference to local prescribing information. Added details on BVY formulations, packaging, labeling, storage conditions, and administration.	Sections 5.2, 5.2.1, 5.2.2, 5.2.3, 5.2.4, and 5.3

11.4. Investigator Signature Page

GILEAD SCIENCES, INC.
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USA

STUDY ACKNOWLEDGMENT

An Umbrella Phase 1b, Open-label, Multi-Cohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1 Substudy-02: GS-1720

Amendment 2, 05 May 2023

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

Name (Printed) PPD Director, Clinical Development	Signature
Date	

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)	Signature
Date	Site Number

Prot GS-US-544-5905-02 amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	05-May-2023 15:21:22