CLINICAL SUBSTUDY-01 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-01: GS-5894
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	162030
EudraCT Number:	Not Applicable
ClinicalTrials.gov Identifier:	Not Available
Indication:	HIV-1 infection
Protocol ID:	GS-US–544–5905-01
Contact Information:	The medical monitor name and contact information will be provided in the Key Study Team Contact List.
Protocol Version/Date:	Original: 03 August 2022 Amendment 1: 27 September 2022

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.

CONFIDENTIALITY STATEMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%CV	percentage coefficient of variation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AUC	area under the concentration versus time curve
$AUC_{0\text{-}168\ h}$	partial area under the concentration versus time curve from time "0" to time "168 h"
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_t	concentration at specified time "t"
CYP	cytochrome P450 enzyme
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
Gilead	Gilead Sciences/Gilead Sciences, Inc.
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IB	investigator's brochure
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
mAbs	monoclonal antibodies
LA	long-acting
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PD	pharmacodynamic
PEP	postexposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PWH	people with HIV
RNA	ribonucleic acid

SAE	serious adverse event
SOC	standard of care
SRT	safety review team
$t_{1/2}$	terminal elimination half-life
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
US	United States

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-01: GS-5894

IND Number: 162030
EudraCT Number: Not applicable
ClinicalTrials.gov Identifier: Not available

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-01 is an open-label, Phase 1b, single-dose/multiple-dose, multicohort study to evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-5894 given as monotherapy in people with HIV-1 (PWH) 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 pre-exposure prophylaxis (PrEP) or postexposure prophylaxis (PEP). Any current or prior receipt of long-acting parenteral ARVs such as monoclonal antibodies (mAbs) 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. 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 another nonnucleoside reverse transcriptase inhibitor (NNRTI)-based standard of care (SOC) ART regimen selected by the investigator. If participants are switching to BVY, a 30-day supply will be given to provide coverage for up to 5 half-lives of GS-5894. Participants will be required to return to the clinic for follow-up visits on Days 18, 25, and 39.

This substudy will enroll up to approximately 5 cohorts with at least 6 participants in each cohort. Participants will be enrolled in Cohort 1 initially and then dosing in subsequent cohorts will proceed after safety review team (SRT) review of emerging data.

The doses and dosing regimen for GS-5894 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 (FIH) study of GS-5894.

Number of Participants Planned: Up to 30 participants

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

Duration of Intervention: Up to 39 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 a non-NNRTI-based 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 initiate a regimen of BVY provided by the sponsor or another non-NNRTI-based SOC ART regimen selected by the investigator. Participants will be required to return to the clinic for visits on Days 18, 25, and 39.

The detailed schedule of procedures for Substudy-01 is provided in Table 1.

Test Product, Dose, and Mode of Administration:

Single or multiple doses of GS-5894 will be administered starting on Day 1. The dose, dose regimen, and meal requirements for administration of GS-5894 in Cohort 1 are provided below. Subsequent cohort dosing, 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. Doses in subsequent cohorts will not exceed the doses indicated below.

Doses of GS-5894 will be administered orally at the clinic under observation by site staff in the morning at approximately the same time each day (in the case of multiple-dose regimens).

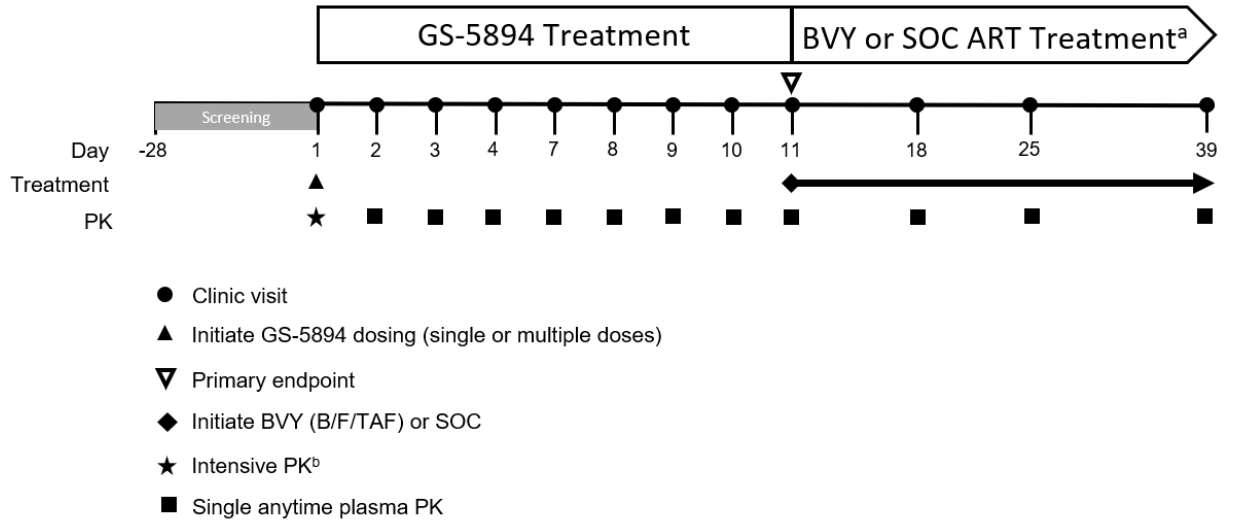
Single or multiple doses of study drug (GS-5894) will be administered orally in the morning with or without regard to food (as appropriate).

- Cohort 1: Single dose of GS-5894 675 mg administered on Day 1 with a high-fat meal

• Cohort 2: Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal) • Cohort 3: Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal) • Cohort 4: Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal) • Cohort 5: Single or multiple doses of GS-5894 up to 2025 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-01 STUDY SCHEMA

Figure 1. Overview of Visits, Dosing, and Key Assessments for Substudy-01



ART = antiretroviral therapy; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); FIH = first in human; 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 another non-NNRTI based SOC ART regimen selected by the investigator.

b Additional intensive PK visits may be required for cohorts with more than one day of dosing of GS-5894.

For Cohort 1, a single dose of 675 mg dose of GS-5894 will be administered on Day 1 with a high fat meal. The doses, dosing regimen (single or multiple doses), and meal requirements for GS-5894 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 FIH study of GS-5894 (Section 3.1.1).

SUBSTUDY-01 STUDY PROCEDURES TABLE

Table 1. Substudy-01 Study Procedures Table

Study Procedure	Screening[a]	D1[b]	D2	D3[b]	D4	D7[b]	D8	D9	D10	D11[b]	D18[b]	D25[b]	D39[b]	ET[c]
Visit Window											**±1D**	**±1D**	**±1D**	
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,h]	X	X		X		X				X	X	X	X	X
Coagulation panel[f,h]	X	X				X				X			X	X
Chemistry[f,h]	X	X		X		X				X	X	X	X	X
Urinalysis[f,h]	X	X		X		X				X	X	X	X	X
Serum pregnancy test[f,i]	X													
Urine pregnancy test[f,i, j]		X											X	X
Serum FSH[f,k]	X													
12-Lead ECG	X	X				X				X			X	X
Intensive plasma PK[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-5894) dosing[o]		X												
BVY dispensation										X				
BVY or SOC administration										X[p] →				

AE = adverse event; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CLcr = creatinine clearance; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; ET = early termination; 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 Chemistry, hematology, coagulation, and urinalysis profiles per Section 6.3.7 of the master protocol.
i Participants assigned female at birth of childbearing potential only.
j 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.
k Serum FSH test is required for participants assigned female at birth and are < 54 years old, not on hormonal contraception, and who have stopped menstruating for ≥ 12 months but do not have documentation of hormonal ovarian failure.
l Intensive PK samples should be collected at these timepoints 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-5894.
m Single anytime PK sampling will occur relative to study drug dosing on Day 1.
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 675-mg dose of GS-5894 administered on Day 1 with a high-fat meal (Section 5.2.4). Subsequent cohort dose, dosing regimens (ie, single or multiple doses), meal requirements (fasted or with a low- 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-01 will evaluate the safety, pharmacokinetics (PK), and antiviral activity of GS-5894 given as monotherapy in people with HIV-1 (PWH), who are either treatment-naive or treatment-experienced but naive to nonnucleoside reverse transcriptase inhibitor (NNRTI) class and have not received any antiretroviral (ARV) therapy (ART) within 12 weeks of screening (full population details provided in Section 4). This is a substudy being conducted as part of the GS-US-544-5905 master protocol.

1.1. Rationale for Substudy-01

Current first-line ART regimens consist of 2 or 3 ARV drugs, often coformulated, allowing a one-pill, once-daily oral treatment regimen; these regimens result in virologic suppression in more than 80% of PWH {Department of Health and Human Services (DHHS) 2018}, {Gunthard 2016}, {European Aids Clinical Society (EACS) 2021}, {World Health Organization (WHO) 2016}. A major factor preventing more widespread success of oral treatment is suboptimal adherence, a primary cause of incomplete viral suppression. There are multiple barriers to adherence, such as inconvenience, side effects, stigma, and discrimination {Enriquez 2011}.

Long-acting (LA) ARV regimens with less frequent dosing, for example LA injectable or oral weekly regimens, have the potential to address challenges with suboptimal adherence and treatment fatigue associated with daily oral therapy and improve success rates while also helping to prevent transmission of HIV.

An oral weekly regimen could benefit individuals who desire an oral regimen but prefer a regimen that can be taken less frequently than daily.

Based on the available PK data (as of 22 June 2022) from the ongoing Phase 1a first-in-human (FIH) study GS-US-544-5906, the median terminal elimination half-life ($t_{1/2}$) of GS-5894 was between 4.77 and 7.96 days. GS-5894 also exhibited high metabolic stability and a slow rate of metabolism in human hepatocytes. With these supporting data, GS-5894 has the potential to be administered orally once weekly and to be combined with other LA agents as part of a combination regimen for the treatment of HIV-1 infection.

1.2. Background on Study Interventions Used in Substudy-01

1.2.1. GS–5894

1.2.1.1. General Information

GS-5894 is a novel NNRTI being developed as a once-weekly oral treatment for HIV-1 infection. In vitro antiviral testing has demonstrated that GS-5894 is a potent and selective nonnucleoside inhibitor of HIV-1 replication, showing strong antiviral activity against clinical isolates from all major HIV-1 subtypes. GS-5894 maintains full antiviral activity against a broad spectrum of HIV-1 mutants resistant to nucleoside reverse transcriptase inhibitors (NRTIs),

protease inhibitors (PIs), and integrase strand-transfer inhibitors (INSTIs).
In addition, reverse transcriptase (RT) mutant viruses that are resistant to the NNRTIs nevirapine and efavirenz remain largely sensitive to GS-5894. With the human $t_{1/2}$, GS-5894 has the potential to be administered orally once weekly and to be combined with other LA agents as part of a combination regimen for the treatment of HIV-1 infection.

For further information on GS–5894, 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-5894

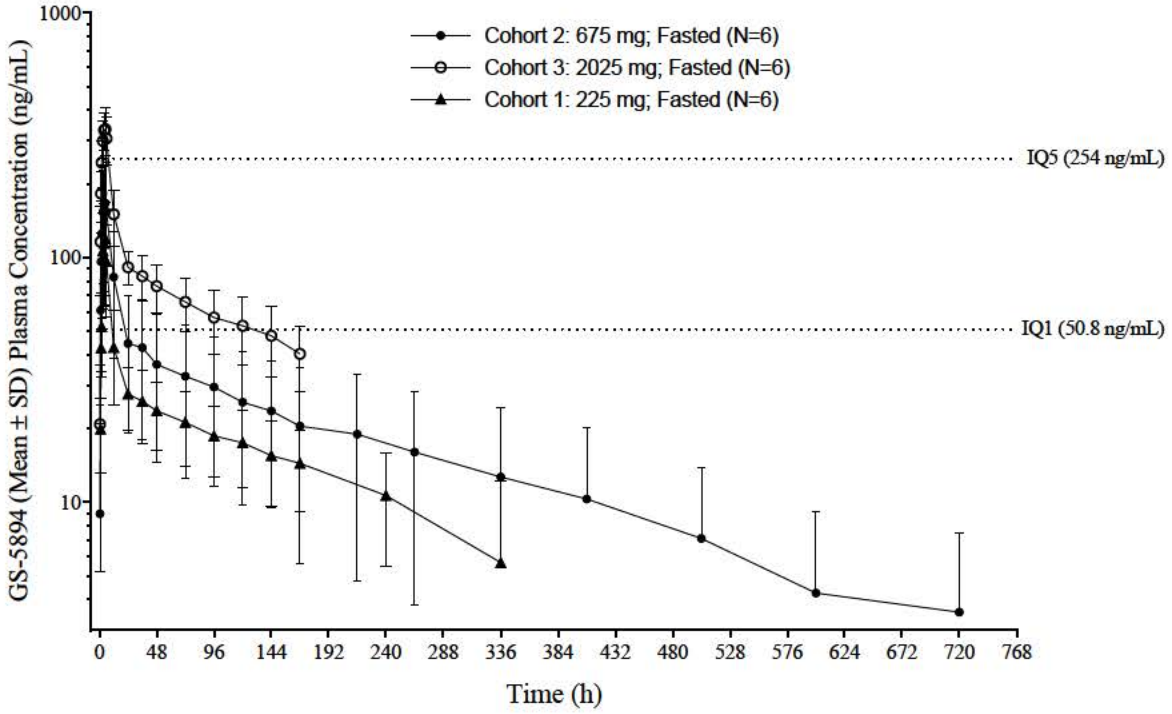
1.2.1.3.1. GS-US-544-5906

Study GS-US-544-5906 is an ongoing, Phase 1a study in healthy volunteers evaluating the safety, tolerability, and PK of single and multiple ascending oral doses of a GS-5894. Twenty-four unique participants across 3 dosing cohorts have received either GS-5894 or placebo (3:1 ratio). Administration of single oral doses of GS-5894 225 mg (Cohort 1), 675 mg (Cohort 2), and 2025 mg (Cohort 3) is complete. In addition, 19 participants completed dosing in the food-effect Cohort 5. Pharmacokinetic sampling for Cohorts 1, 2, and 3, and Cohort 5 (through at least Day 7) is complete. Pharmacokinetic data available as of 22 June 2022 are summarized below.

Preliminary PK Summary:

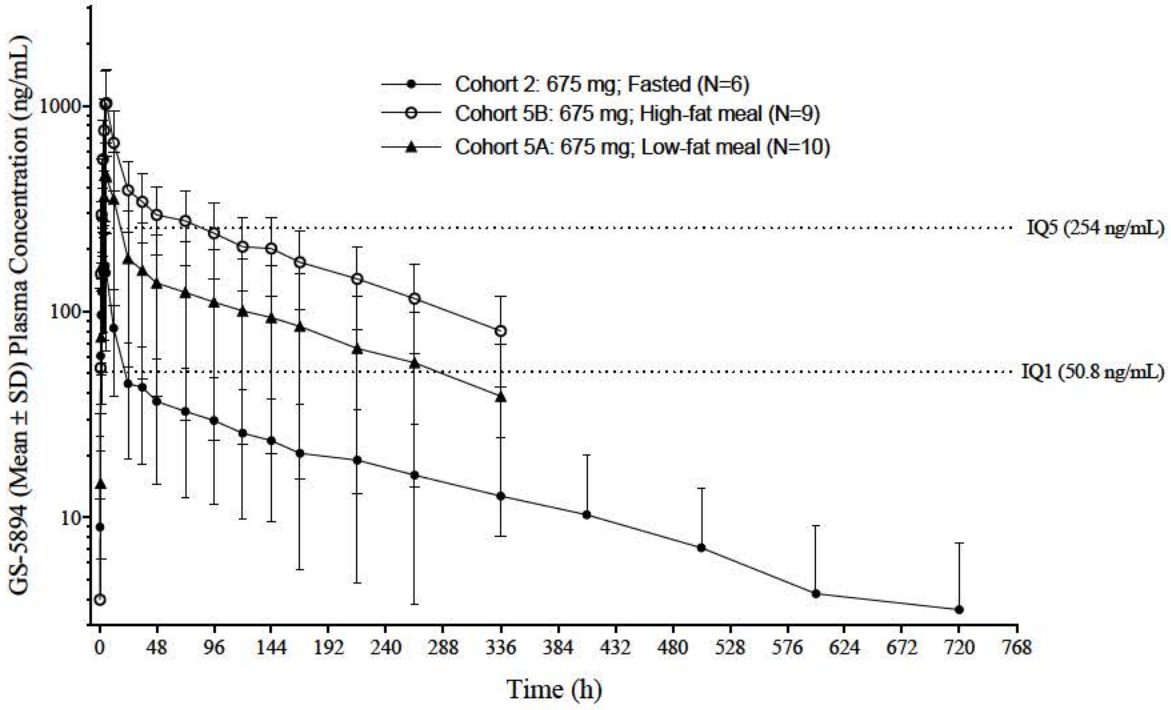
Preliminary GS-5894 plasma concentration-time profiles and preliminary PK parameters after administration of single oral doses of 225 mg (Cohort 1), 675 mg (Cohort 2), and 2025 mg (Cohort 3) in the fasted condition, as well as 675 mg with a low- or high-fat meal (Cohort 5) are presented in Figure 2, Figure 3, and Table 2 and Table 3. Median time to maximal plasma concentrations of GS-5894 (C_{max}) occurred between 3.5 and 5.5 hours (median T_{max}). A 9-fold increase in dose (from 225 mg to 675 mg and then 2025 mg) resulted in only 2.8-fold higher C_{max} and 3.2-fold higher $AUC_{0\text{-}168h}$. The increases in C_{max} and $AUC_{0\text{-}168h}$ were less than dose proportional, suggesting GS-5894 exhibits solubility-limited absorption. GS-5894 showed a positive food effect; C_{max} and $AUC_{0\text{-}168h}$ following a 675 mg dose with a low-fat meal were 3-fold higher and 3.6-fold higher compared with a 675 mg dose in the fasted condition. Similarly, C_{max} and $AUC_{0\text{-}168h}$ following a 675 mg dose with a high-fat meal were 6.1-fold higher and 7.7-fold higher compared to a 675 mg dose in the fasted condition.

Figure 2. **GS-US-544-5906: Preliminary Mean (SD) GS-5894 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-5894 (N = 6 per Cohort) in the Fasted Condition**



IQ1, 5 = inhibitory quotient 1- or 5-fold higher than the protein adjusted EC95 against wild type HIV-1 virus ($paEC_{95}$; 50.8 ng/mL)

Figure 3. **GS-US-544-5906: Preliminary Mean (SD) GS-5894 Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral GS-5894 675 mg in the Fasted Condition as well as with a Low-Fat or High-Fat Meal**



IQ1, 5 = inhibitory quotient 1- or 5-fold higher than the protein adjusted EC95 against wild type HIV-1 virus ($paEC_{95}$; 50.8 ng/mL)

Table 2. GS-US-544-5906: Preliminary Plasma PK Parameters of GS-5894 Following Single-Dose Administration of Oral GS-5894 (N = 6 per Cohort) in the Fasted Condition

Parameter	Cohort 1 (225 mg, Fasted)	Cohort 2 (675 mg, Fasted)	Cohort 3 (2025 mg, Fasted)
C_{max} (ng/mL)	123 (38.9)	179 (51.3)	349 (19.3)
T_{max} (h)	5.00 (3.00, 5.00)	3.50 (2.75, 4.25)	4.50 (4.00, 5.25)
C_{last} (ng/mL)	8.98 (36.6)	6.73 (10.0)	40.3 (30.3)
T_{last} (h)	288 (240, 336)	660 (318, 720)	168 (168, 168)
$AUC_{0\text{-}168\ h}$ (h•ng/mL)	4080 (33.3)	6520 (57.5)	12900 (22.9)
AUC_{Inf} (h•ng/mL)	8350 (50.4)	14200 (53.4)	20200 (25.8)
AUC_{Extrap} (%)	29.8 (36.7)	19.0 (60.2)	35.0 (18.6)
$t_{1/2}$ (d)	6.68 (5.30, 10.4)	7.96 (6.28, 12.7)	4.77 (4.20, 6.31)

d = days; h = hour; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile. 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 timepoints.

Table 3. GS-US-544-5906: Preliminary Plasma PK Parameters of GS-5894 Following Single-Dose Administration of Oral GS-5894 675 mg in the Fasted Condition as well as with a Low-Fat or High-Fat Meal

Parameter	Cohort 2 (225 mg, Fasted)	Cohort 5A (675 mg With Low-fat Meal)	Cohort 5B (675 mg With High-fat Meal)
C_{max} (ng/mL)	179 (51.3)	534 (38.1)	1090 (39.3)
T_{max} (h)	3.50 (2.75, 4.25)	5.50 (4.00, 7.50)	5.00 (5.00, 9.00)
C_{last} (ng/mL)	6.73 (10.0)	39.3 (75.8)	80.4 (46.5)
T_{last} (h)	660 (318, 720)	336 (336, 336)	336 (336, 336)
$AUC_{0\text{-}168\ h}$ (h•ng/mL)	6520 (57.5)	23700 (68.4)	50200 (37.6)
AUC_{Inf} (h•ng/mL)	14200 (53.4)	43200 (69.4)	88200 (40.0)
AUC_{Extrap} (%)	19.0 (60.2)	21.3 (36.8)	19.7 (35.1)
$t_{1/2}$ (d)	7.96 (6.28, 12.7)	6.52 (5.31, 8.35)	5.62 (4.89, 7.31)

d = days; h = hour; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile. 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 timepoints.

Safety Summary:

In a preliminary blinded review of safety data as of 28 June 2022 (n = 43), no deaths, serious adverse events (SAEs), Grade 2 or higher adverse events (AEs), or discontinuations due to AEs have been reported to date. Two participants experienced AEs related to study drug; one in Cohort 2 (675 mg GS-5894) with proteinuria at Day 2 (resolved at Day 7) and one in Cohort 5 (675 mg GS-5894, low-fat/moderate-calorie breakfast) with nausea, diarrhea, and vomiting at Day 1 (all resolved on same day).

Grade 3 laboratory abnormalities were reported for 3 participants and were not clinically relevant (creatinine clearance: 2 participants; low-density lipoprotein cholesterol: 1 participant).

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

1.3. Rationale for Dose Selection of Study Drug

Selection of the GS-5894 doses for this study takes into consideration the available safety, tolerability, and PK data for GS-5894 from the ongoing FIH study with oral single and multiple ascending doses in healthy volunteers (Study GS-US-544-5906), as well as emerging preliminary safety and antiviral activity data in this substudy.

As of 28 June 2022, 43 participants (37 active and 6 placebo) have received a single oral dose of GS-5894 (225 to 2025 mg) or placebo-to-match. All participants have completed at least 7 days of follow up. As of the data cut-off date (28 June 2022), there were no deaths, SAEs, Grade 2 or higher AEs, or discontinuations due to AEs. GS-5894 was generally well-tolerated.

Available PK data from Study GS-US-544-5906 (as of 22 June 2022), as shown in Figure 2 and Figure 3, as well as in Table 2 and Table 3, demonstrates that the highest C_{max} and $AUC_{0\text{-}168h}$ were observed following a 675-mg dose with a high-fat meal (Cohort 5B). Exposure margins based on observed data following 675 mg with a high-fat meal (Cohort 5B) were 14-fold and 11-fold for $AUC_{0\text{-}168h}$ and 5-fold and 7-fold for C_{max} compared with the dog and mouse NOAELs, respectively. Following a 675 mg dose with a high-fat meal, mean GS-5894 concentrations achieved target IQ5 (that is 5-fold higher than the protein adjusted EC_{95} against wild type HIV-1 virus [$paEC_{95}$; 50.8 ng/mL]) rapidly, and concentrations were maintained (> IQ5) through 72 hours postdose; mean GS-5894 concentrations at Day 8 and Day 12 were 173.5 ng/mL (maintained above IQ3) and 115.5 ng/mL (maintained above IQ2), respectively. Based on these results, 675 mg with a high-fat meal was selected for evaluation in Cohort 1 of this substudy. Higher/lower doses (compared to Cohort 1 dose) may be evaluated in subsequent cohorts to target a range of IQ values to characterize the PK/PD relationship between GS-5894 PK parameters and changes in HIV-1 viral load.

1.4. Risk/Benefit Assessment for Substudy-01

Potential risks to participants could include prolonged exposure for several weeks to subtherapeutic concentrations of the study drug, which can lead to HIV-1 developing resistance to the study drug and potentially to the study drug class and could limit future treatment options. Strategies to mitigate this risk and additional risk/benefit assessments applicable to Substudy-01 and GS-5894 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-01 is an open-label, Phase 1b, single/multiple-dose, multicohort study to evaluate the safety, PK, and antiviral activity of GS-5894 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 pre-exposure prophylaxis (PrEP) or postexposure prophylaxis (PEP). Any current or prior receipt of long-acting parenteral ARVs such as monoclonal antibodies (mAbs) 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). After assessments on Day 11 or upon early termination (ET), participants will initiate a regimen of Biktarvy® (bictegravir [BIC, B]/emtricitabine [FTC, F]/tenofovir alafenamide [TAF]; BVY) provided by the sponsor, or other non-NNRTI based standard of care (SOC) ART regimen selected by the investigator. If participants are switching to BVY, a 30-day supply will be given to provide coverage for up to 5 half-lives of GS-5894. Participants will be required to return to the clinic for follow-up visits on Days 18, 25, and 39. Overnight fasting (≥ 6 hours) is required for laboratory analyses prior to visit on Days 1, 3, 7, 11, 18, 25, and 39.

The selection of doses and dosing regimen for GS-5894 is described in Section 3.1.1.

This substudy will enroll up to approximately 5 cohorts with at least 6 participants in each cohort. Participants will be enrolled in Cohort 1 initially and then dosing in subsequent cohorts will proceed after safety review team (SRT) review of emerging data as described in Section 3.1.1.

Sequential enrollment in cohorts and order of assignment to substudies is 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-5894 will begin with Cohort 1. The dose and regimen of GS-5894 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 this Substudy-01 for 39 days.

Participants will receive single or multiple doses of GS-5894 starting on Day 1. Participants will then initiate a BVY or another non-NNRTI-based SOC ART regimen on Day 11 following study assessments to provide coverage for up to 5 half-lives of GS-5894. Participants will be required to return to the clinic for follow-up visits on Days 18, 25, and 39.

3.3. Substudy-01-Specific Discontinuation Criteria

Substudy criteria for early discontinuation for the 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

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

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection for Substudy-01

In Substudy-01, up to approximately 5 cohorts of at least 6 participants each will be enrolled. Participant replacement is described in Section 4.1.1 of the master protocol.

4.2. Substudy-01-Specific Inclusion Criteria

Inclusion criteria applicable to all substudies is 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:

S01-1. 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 a non-NNRTI-based SOC ART regimen selected by the investigator on Day 11 or upon ET.

S01-2. Willing and able to comply with meal requirements on dosing days.

4.3. Substudy-01-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:

S01-1. Requirement for ongoing therapy with any prohibited medications listed in Section 5.3.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment and Treatment Code Access

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

5.2. Description and Handling of GS-5894 and Commercially Available BVY

Commercially available BVY will be provided by the sponsor for use during the study as applicable. Further information regarding storage and handling are available in the prescribing information for the commercial BVY product.

The description and handling of GS-5894 is described below.

5.2.1. Formulation

GS-5894 tablets are available in strengths of 75 and 600 mg. GS-5894 tablets, 75 mg, are round, plain-faced, film-coated, gray-colored tablets. GS-5894 tablets, 600 mg, are oval, plain-faced, film-coated, gray-colored tablets. In addition to the active ingredient, GS-5894 tablets, 75 mg and 600 mg, also contain microcrystalline cellulose, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and ferrosoferric oxide.

5.2.2. Packaging and Labeling

GS-5894 tablets are packaged in white, high-density polyethylene bottles containing silica gel desiccant and polyester coil packing material. Each bottle is enclosed with a white continuous-thread, child-resistant, polypropylene screw cap with an induction-sealed, aluminum-faced liner.

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

5.2.3. Storage and Handling

GS-5894 tablets should be stored below 30 °C. Storage conditions are specified on the label. GS-5894 should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of GS-5894 and proper identification, the drug product should not be stored in a container other than the container in which it is supplied.

5.2.4. Dosage and Administration

Single or multiple doses of GS-5894 will be administered starting on Day 1. The dose, dose regimen, and meal requirements for administration of GS-5894 in Cohort 1 are provided in Table 4. Subsequent cohort dose, dosing regimens (ie, single or multiple doses), meal requirements (fasted or with a low- 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 the doses indicated in Table 4.

Doses of GS-5894 will be administered orally at the clinic under observation by site staff in the morning at approximately the same time each day (in the case of multiple-dose regimens).

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) will be initiated 30 minutes prior to study drug administration, respectively. Participants will be administered GS-5894 at or within 5 minutes of participants consuming the meal.

Table 4. GS-5894 Dosage by Cohort

Cohort	Treatment
Cohort 1	Single 675 mg dose administered on Day 1 with a high-fat meal
Cohort 2	Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 3	Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 4	Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal)
Cohort 5	Single or multiple doses of GS-5894 up to 2025 mg administered in the fasted condition or with food (low-fat or high-fat meal)

5.3. Prior and Concomitant Medications

See Section 5.3 of the master protocol for information on prior and concomitant medication rules applicable to all substudies including restricted medications through Day 11.

Medications prohibited from after the last dose of study drug on Day 11 through Day 39 in this substudy are presented in Table 5. Metabolism of GS-5894 was detectable with cytochrome P450 enzyme (CYP)3A in-vitro. Concomitant use of GS-5894 with some medications or herbal/natural supplements that are inhibitors of CYP3A may result in increased exposure of GS-5894. On the other hand, concomitant use of GS-5894 with some medications or herbal/natural supplements that are inducers of CYP3A may result in decreased exposure of GS-5894. Representative strong CYP3A inhibitors and strong/moderate CYP3A inducers listed in Table 5 are recommended to be excluded while participating in this substudy (Day 11 through Day 39). This table is not exhaustive and if there are medications not included in Table 5,

the investigator should reach out to the sponsor for guidance to use any concomitant medication while participants are on the substudy.

Table 5. Examples of Medications Prohibited From Day 11 Through Day 39 Because of the Potential for Pharmacokinetic Drug-Drug Interaction With GS-5894[a]

Medication Class	Prohibited Medications
ARVs	Amprenavir, lopinavir, ritonavir, indinavir, saquinavir, nelfinavir, ritonavir- or cobicistat-containing regimens, boceprevir, telaprevir, efavirenz, etravirine, and nevirapine
Antiandrogens	Apalutamide, enzalutamide
Antibiotics	Clarithromycin, rifampin, rifapentine, telithromycin, troleandomycin
Antifungals	Itraconazole, ketoconazole, voriconazole, posaconazole
Herbal Medications	St. John's wort

ARVs = antiretrovirals
a This table represents examples of the most common concomitant medications and is not meant to be exhaustive. If the investigator is unsure if a medication is allowed per protocol, he/she should consult with the sponsor.

From Day 11 through the last visit, the investigator should follow the current United States Prescribing Information to inform the use of concomitant/prohibited medications for BVY {BIKTARVY 2021} or other ART taken as the SOC by the individual participant.

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

Guidance related to accountability, return, and disposal for study drug supplies (study drug [GS-5894 for this study] 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-01 are listed in the sections below. The timepoints for study procedures are specified in Table 1. Substudy-specific ICFs will be required for Substudy-01.

6.1. Instructions for Study Procedures

6.1.1. Pharmacokinetics

Blood samples will be collected to determine GS-5894 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 the participant's last visit is described in Section 6.3.9.1.3 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-5894 is described below and included in Appendix 11.2. Pregnancy precautions, definition of female of childbearing potential, and contraceptive requirements specific to GS-5894 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 and 4 laboratory abnormality (eg, creatine kinase [CK] elevation after strenuous exercise, triglyceride elevation that is nonfasting or that can be medically managed). Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

- Grade 3 or 4 clinical events if considered unrelated to the study drug may not require dose interruption; continuation of the investigational product 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 to be related to the 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 to be related to the study drug, 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 occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

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 AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the 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

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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 (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female 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-5894 is contraindicated in pregnancy as a malformative effect is unknown. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. GS-5894 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 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 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 39 days after the last study drug dose.

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 1 of the following methods of birth control listed below:

- Nonhormonal intrauterine device (IUD)
- 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 39 days after the last study drug dose. 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

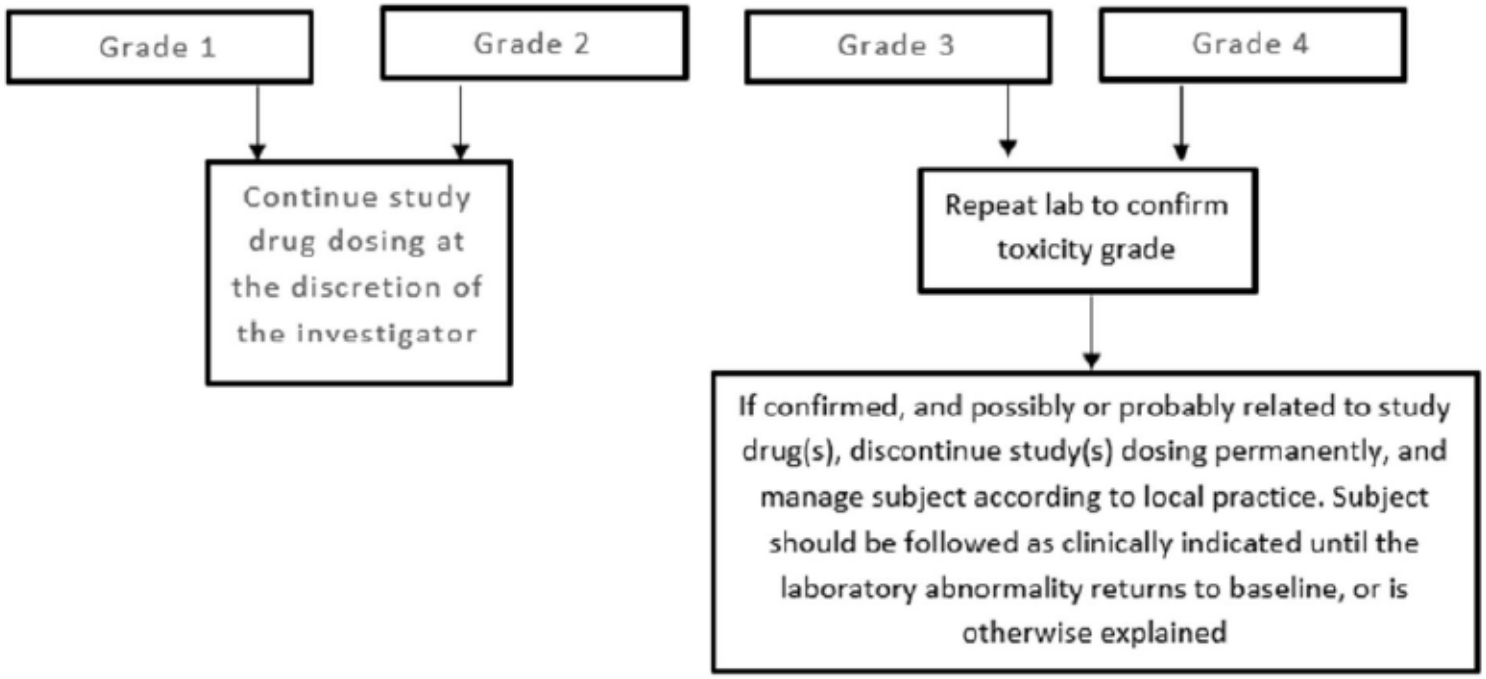
Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

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 39 days after the last study drug dose.

Participants assigned male at birth whose partner has become pregnant or suspects they are pregnant from start of study until 39 days after the last study drug dose 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. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
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.
27 September 2022

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

PPD

Name (Printed)
Exec 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-544-5905-01 amd-1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	27-Sep-2022 21:43:49