STATISTICAL ANALYSIS PLAN

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
Name of Test Drug:	GS-5894
Study Number:	GS-US–544–5905-01
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BVY	Biktarvy ® (bictegravir/emtricitabine/tenofovir alafenamide)
CCG	eCRF Completion Guidelines
CD4	Cluster of Differentiation type 4
CI	confidence interval
CK	creatine kinase
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic Case Report Form
$eGFR_{CG}$	estimated Glomerular Filtration Rate (Cockcroft Gault formula)
ET	early termination
FAS	Full Analysis Set
FIH	first-in-human
Hb	hemoglobin
HIV-1	Human Immunodeficiency Virus Type 1
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	Identification
LLT	lower-level term
LOQ	limit of quantitation
mAbs	monoclonal Antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA Search Term
NLP	Natural Language Processing
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PD	Pharmacodynamic
PEP	Post-Exposure Prophylaxis
PK	pharmacokinetic
PrEP	Pre-Exposure Prophylaxis
PT	preferred term
PWH	people with HIV

Q1, Q3	first quartile, third quartile
RNA	ribonucleic acid
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SMQ	Stardardized MedDRA Query
SOC	system organ class
SRT	Safety Review Team
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
%CV	coefficient of variation, defined as ratio of standard deviation to the mean

PHARMACOKINETIC ABBREVIATIONS

AUC	Area under the plasma/serum concentration versus time curve
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve from time zero to infinity
$\%AUC_{exp}$	Percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_t	concentration at time t
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
V_z/F	Apparent volume of distribution of the drug
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-544-5905-01 (Master Protocol GS-US-544-5905, Substudy 01). This SAP is based on the Study GS-US-544-5905 master protocol Amendment 2 dated 24 February 2023, Substudy GS-US-544-5905-01 protocol Amendment 1 dated 27 September 2022, and the electronic case report form (eCRF) for Study GS-US-544-5905-01. The SAP will be finalized before Study GS-US-544-5905-01 database finalization. Any changes made after the finalization of the SAP will be documented in the GS-US-544-5905-01 CSR.

1.1. Study Objectives

The primary objective of this substudy is as follows:

To evaluate the short-term antiviral activity of GS-5894 with respect to the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Day 11 in people with HIV-1 (PWH) who are ARV treatment-naive or treatment-experienced but naive to the investigational ARV drug class (non-nucleoside reverse transcriptase inhibitor [NNRTI]).

The secondary objectives of this substudy are as follows:

- To evaluate the short-term antiviral activity of GS-5894 in reducing plasma HIV-1 RNA (log_{10} copies/mL)
- To investigate the safety and tolerability of GS-5894 by dose cohort
- To characterize the plasma pharmacokinetics (PK) of GS-5894
- To characterize the PK/pharmacodynamic (PD) relationship between the exposure of GS-5894 and the viral dynamics of HIV-1
- To determine the number and percentage of participants who achieve HIV-1 RNA < 50 copies/mL of the HIV-1 RNA assay by Day 11 at each dose level
- To examine the emergence of restance to the NNRTI drug class

1.2. Study Design

This is an open-label Phase 1b, single or multiple dose, multicenter, substudy to an umbrella study designed to evaluate 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 under investigation (NNRTI). Participants will not have received any ARVs within 12 weeks of screening, including medications received for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Any current or prior receipt of long-acting parenteral ARVs including: mAbs targeting HIV-1, injectable cabotegravir, or injectable rilpivirine is exclusionary.

This umbrella study will consist of a master protocol describing information relevant to all substudies; and each novel compound will have its own substudy. GS-5894 will be the first substudy protocol (GS-US-544-5905-01). This flexible clinical study design allows for opening new substudies as new agents become available and closing substudies with study drugs that demonstrate minimal clinical activity and/or unacceptable toxicity.

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 NNRTI-based standard of care 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 dose level and dosing regimen for study drug 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) for this substudy, and/or relevant and available safety and PK data from the ongoing Phase 1a first-in-human (FIH) study for GS-5894.

Assessments will be conducted per the schedule of assessment table (see Schedule of Assessments, Appendix 1).

1.3. Sample Size and Power

A sample size of 6 to 8 participants in each dose cohort will provide 83% to 94% power to detect a treatment difference of 1.0 $\log_{10}$ copies/mL in the change from baseline in HIV-1 RNA at Day 11 between at least one of the study drug dose groups and the historical placebo group (N = 21). In this power analysis, it is assumed that a SD for the change from baseline in HIV-1 RNA at Day 11 is 0.662 $\log_{10}$ copies/mL for each study drug dose group and 0.359 $\log_{10}$ copies/mL for the placebo group, and a 2-sided t-test is conducted at an alpha level of 0.05. Standard deviations were estimated from historical Phase 1b studies conducted by the sponsor (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072). The maximum SD from treatment groups was used for the study drug dose group and SD from the pooled placebo group was used for the placebo group.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

Before the final analysis for each substudy, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program of GS-5894.

2.2. Dose Escalation Analysis

A safety review team (SRT) will review the data from this substudy after all participants from Cohort 1 complete their Day 11 visit. The SRT review will include cumulative safety and HIV-1 RNA data through the primary endpoint (Day 11) and available PK data from Cohort 1 of this substudy; and/or relevant and available safety and PK data from the Phase 1a FIH study for GS-5894 (as appropriate). This initial SRT review will facilitate decision-making for dose level, dosing regimen (including whether GS-5894 study drug will be taken in a fasted state, or with a low-fat or high-fat meal) and timing of dosing for Cohorts 2 to 5. Further CCI reviews by the SRT may be needed to inform on dose selection for Cohorts 2 to 5 (and/or additional cohort[s], as applicable).

2.3. Final Analysis

The final analysis will be performed after all participants in Substudy 01 have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint (change from baseline in HIV-1 RNA [$\log_{10}$ copies/mL] at Day 11) will be conducted at the time of the final analysis and will be tested at the 0.05 significance level (2-sided test).

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and will be sorted by participant identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The GS-5894 cohort to which participants were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion, will be summarized by GS-5894 cohort and overall.

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who received a study participant ID number in the substudy after screening.

All Enrolled Analysis Set is the primary analysis set for by-participant listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all participants who are enrolled and receive a full dose[s] of GS-5894 study drug in this substudy. Participants with major eligibility violations that are identifiable based on pre-enrollment characteristics may be excluded. Participants will be grouped according to the GS-5894 cohort assigned at enrollment.

Participants who were randomized and assigned to receive placebo from 3 historical Gilead Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be used as a historical control through Study Day 11 for only the HIV-1 RNA endpoints.

The Full Analysis Set will be the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of GS-5894 study drug in this substudy. Participants who received treatment other than that assigned at enrollment will be analyzed according to the treatment that they received.

All data collected on/after first dose date of GS-5894 during the substudy will be included in the safety summaries.

The Safety Analysis Set is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

The PK Analysis Set includes all participants who are enrolled, receive any dose of GS-5894 study drug in this substudy, and have at least 1 nonmissing post baseline concentration value for GS-5894 study drug.

This is the primary analysis set for all PK analyses.

3.1.5. Pharmacokinetic/Pharmacodynamic Analysis Set

The PK/PD Analysis Set will include all participants who are in the FAS for this substudy and have a nonmissing PK parameter (for PK parameter included in analysis) and a nonmissing value for change from baseline at Day 11 in plasma HIV-1 RNA (log_{10} copies/mL). This is the primary analysis set for PK/PD analysis.

A secondary analysis of PK/PD will be performed for the secondary endpoint change from baseline to Day 8 in HIV-1 RNA (log_{10} copies/mL) and will include all participants who are in the FAS for this substudy and have a nonmissing PK parameter (for PK parameter included in analysis) and a nonmissing value for change from baseline at Day 8 in plasma HIV-1 RNA (log_{10} copies/mL).

Analysis of these endpoints will be described in a separate PK/PD SAP.

3.2. Participant Grouping

For analyses based on the FAS, participants will be grouped according to the GS-5894 cohort to which they were enrolled. Data from participants who were randomized and assigned to receive placebo from 3 historical Gilead Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be pooled to form a historical placebo group for HIV-1 RNA endpoints through Study Day 11. For all other analyses, participants will be grouped according to the actual GS-5894 treatment received in this substudy.

For enrollment, disposition, protocol deviations, demographics, baseline disease characteristics, AEs, vital signs, concomitant medications, and laboratory data summaries, an additional total column for all GS-5894 participants will be included.

For efficacy and PK summaries and the ECG shift table, a total column for all GS-5894 participants will not be included.

3.3. Strata and Covariates

No covariates will be included in efficacy analyses.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroups for efficacy or safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made in this proof-of-concept study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) from the demographic eCRF will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (e.g., change from baseline in HIV-1 RNA will be performed on the $\log_{10}$ transformed data) or nonparametric analysis methods may be used.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics for intensive PK concentrations:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug (or first dose date of placebo for placebo historical control group [HIV-1 RNA data only]) and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

Baseline is defined as the last available value collected on or prior to the first dose date (and time, where applicable) of study drug (i.e., prior to taking first dose of study drug).

Postbaseline is defined as any value collected after the first dose of study drug.

Last Study Date is the latest of clinic visit dates and laboratory visit dates, including all follow-up visits for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF.

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for HIV-1 RNA are provided in Table 3-1; for hematology, chemistry, urinalysis, and $eGFR_{CG}$ in Table 3-2; for vital signs and weight in Table 3-3; for ECGs and coagulation in Table 3-4; and CD4 cell count and percentage in Table 3-5.

Table 3-1. Analysis Visit Windows for HIV-1 RNA

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 2	2	2	2
Day 3	3	3	3
Day 4	4	4	5
Day 7	7	6	7
Day 8	8	8	8
Day 9	9	9	9
Day 10	10	10	10
Day 11	11	11	11
Day 18	18	12	21
Day 25	25	22	32
Day 39	39	33	(none)

Each cohort for GS-5894 will be compared to the historical placebo control group through Study Day 11.

The percentage of participants with HIV-1 RNA < 50 copies/mL will be displayed by GS-5894 cohort at Day 11 (last value prior to starting standard of care) and at Days 18, 25, and 39.

Table 3-2. Analysis Visit Windows for Hematology, Chemistry (including Thyrotropin), Urinalysis and $eGFR_{CG}$

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	5
Day 7	7	6	9
Day 11	11	10	11
Day 18	18	12	21
Day 25	25	22	32
Day 39	39	33	(none)

Table 3-3. Analysis Visit Windows for Vital Signs and Weight

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 2*	2	2	2
Day 3	3	3	3
Day 4	4	4	5
Day 7	7	6	9
Day 11	11	10	11
Day 25	25	12	32
Day 39	39	33	(none)

*Weight is not collected per protocol on Study Day 2. Any weight collected on Day 2 will be considered for Day 3.

Table 3-4. Analysis Visit Windows for ECGs and Coagulation Tests

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 7	7	2	9
Day 11	11	10	11
Day 39	39	12	(none)

Table 3-5. Analysis Visit Windows for CD4 Cell Count and Percentage

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 11	11	2	11
Day 18	18	12	21
Day 25	25	22	32
Day 39	39	33	(none)

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dose of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data (except for HIV-1 RNA, see below), or the measurement with the lowest severity (i.e., normal will be selected over abnormal for safety ECG findings) for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected (with the exception of CD4+ cell count and CD4% in which the latest record will be selected and HIV-1 RNA level [see below]).
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data (except for HIV-1 RNA, see below) and the worst severity will be taken for categorical data, unless otherwise specified.
- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both “Roche COBAS 6800” and “Roche COBAS 6800 Repeat” (i.e., the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the “Roche COBAS 6800 Repeat” will be selected for analysis purposes; otherwise, if there are multiple “Roche COBAS 6800” records with the same collection time, the geometric mean will be taken for analysis purposes.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of key study dates for substudy 01 will present the dates for: 1) first participant screened 2) first participant enrolled 3) last participant enrolled 4) last participant last visit for primary endpoint [Day 11] and 5) last participant last visit for clinical study report.

A summary of participant enrollment in this substudy will be provided by GS-5894 cohort (and overall) for each country, and investigator within country. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants enrolled for that column.

A summary of participant disposition will present the number of participants screened for this substudy (denoted by an "A" contained within the participant screening number under the master protocol) and the number of participants who met all eligibility criteria but were not enrolled with the reasons that participants were not enrolled. An additional summary of participant disposition for participants in the All Enrolled Analysis Set will be provided by GS-5894 cohort and overall. The number and percentage of participants in each of the categories listed below will be summarized:

- All Enrolled Analysis Set
- Safety Analysis Set
- Full Analysis Set
- PK Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-participant listings will be provided by participant ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation (including those related to coronavirus disease 2019 [COVID-19])
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Analysis set status (participants excluded from any of the analysis sets)

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug. Study drug administration was performed at the study site; adherence will not be summarized.

4.2.1. Study Drug Exposure and Duration on Study

Exposure to GS-5894 will be either "Single dose of GS-5894 (Day 1)" or "Single dose of GS-5894 (Days 1 and 2)" and will be summarized based on data collected on the Study Drug Administration eCRF.

Duration on sponsor-provided Biktarvy® (BVY) as standard of care will be summarized using descriptive statistics, and will be calculated as: (last dose date BVY – first dose date of BVY) + 1. The start and stop dates for BVY administered as standard of care are collected on the ARV eCRF with subcategory of "CURRENT". Records with a BVY start date on or after the last date in study will be excluded from calculations.

The number (i.e., cumulative counts) and percentage of participants on SOC for at least the following number of days will be summarized: Day 7, Day 14, Day 21, Day 28. For the final analysis, a ± 1 day window will be applied for the Day 28 category for Biktarvy® (allows for the Day 39 [on Study] protocol specified visit window and participants starting SOC on Day 11).

Duration on study (in days) will be defined as last date in study minus first dosing date plus 1. Last Study Date is the latest of clinic visit dates and laboratory visit dates, including all follow-up visits for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF.

Duration on study (in days) will be summarized using descriptive statistics and using the number (i.e., cumulative counts) and percentage of participants still on study through each study visit: Day 1, Day 2, Day 3, Day 4, Day 7, Day 8, Day 9, Day 10, Day 11, Day 18, Day 25, and Day 39. For the final analysis, a ± 1 day window will be applied for the Day 39 category to allow for the Day 39 protocol specified visit window.

Summaries will be provided by GS-5894 cohort (and overall) for the Safety Analysis Set. Exposure data for GS-5894 study drug will be listed.

No formal statistical testing is planned.

Biktarvy is provided as standard of care by the Sponsor during the follow-up period and dispensing information is recorded on the Accountability eCRF. Accountability data for Biktarvy will be listed.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study will be listed regardless of whether they were exempted by the sponsor or not. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that the participant did not meet.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by GS-5894 cohort and overall for the Safety Analysis Set.

A by-participant listing will be provided for those participants with important protocol deviations.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the COVID-19 pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable. If there are no COVID-19 events, this listing will not be produced.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 3.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be determined through a COVID-19 Standardized MedDRA Query (SMQ) narrow search or MedDRA Search Term (MST) and will be included in analyses of AEs if applicable. A by-participant listing of AEs of COVID-19 will be provided, if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age, sex at birth, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by GS-5894 cohort and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include HIV-1 RNA (log_{10} copies/mL), CD4 cell count (/μL), CD4 percentage (%), mode of infection (HIV risk factors), HIV disease status (AIDS, asymptomatic, or symptomatic HIV infection), years since HIV-1 diagnosis, years since starting HIV-1 treatment, resistance to any of the 4 ARV classes (yes, no) with a count of the number of subjects with resistance to each ARV class [NRTI, NNRTI, PI, and/or INSTI]), and ART status (ART-experienced or ART-naïve). These baseline characteristics will be summarized by GS-5894 dose group and for all GS-5894 participants using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

Note: If only the month and year are collected for "date of HIV-1 diagnosis" and/or "start date of HIV-1 treatment", the day will be set to '01' when imputing the full date. If both the day and month are missing, then '01 July' will be used for the day and month unless the full imputed date is after the first dose date of GS-5894 study drug. If HIV-1 diagnosis date or HIV-1 treatment start date is imputed to be after the first dose date of GS-5894 study drug, set the imputed HIV-1 diagnosis date or treatment start date to the date of first dose of GS-5894 to avoid having a negative duration.

A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will be coded using the MedDRA dictionary.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Day 11.

Historical HIV-1 RNA data for placebo participants from 3 sponsor Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be combined to form a single placebo group for the purpose of HIV-1 RNA analysis through Study Day 11. For Study GS-US-200-4072, HIV-1 RNA (log_{10} copies/mL) collected on Day 10 will be used for "Day 11" since HIV-1 RNA was not collected on Day 11 for this study. Each GS-5894 cohort will be compared to the pooled placebo group with respect to the primary efficacy endpoint, the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Day 11, using the 2-sided t-test conducted at an alpha level of 0.05. The analysis will be conducted using the FAS.

6.2. Secondary Efficacy Endpoints

6.2.1. Change from Baseline in Plasma HIV-1 RNA (log_{10} copies/mL) at Day 8

The secondary efficacy endpoint change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Day 8 will be analyzed using the same methods used for the primary endpoint. For study GS-US-120-0104, HIV-1 RNA (log_{10} copies/mL) collected on Day 7 will be used for "Day 8" since HIV-1 RNA was not collected at Day 8 for this study.

6.2.2. Correlation of PK Parameter(s) and Primary Endpoint

PK/PD analysis will be described in a separate PK/PD SAP.

6.2.3. Percentage of Participants Ever Achieving HIV-1 RNA < 50 copies/mL Postbaseline up to Day 11

The number and percentage of participants ever achieving HIV-1 RNA < 50 copies/mL postbaseline up to Day 11 will be summarized by GS-5894 cohort and for the placebo control group (using the FAS). For historical placebo control participants in study GS-US-120-0104 with HIV-1 RNA values analyzed using the HIV PCR Stand., 1.5 Cobas-CL assay with a LLOQ of 400 copies/mL, a value less than LLOQ (i.e., < 400 copies/mL) was counted as meeting the endpoint (HIV-1 RNA < 50 copies/mL). A Fisher's exact test will be used to compare each GS-5894 cohort to the historical placebo group if at least 1 participant has HIV-1 RNA < 50 copies./mL postbaseline up to Day 11.

6.2.4. Percentage of Participants with Emergence of NNRTI Resistance

Percentage of participants with any emergence of resistance to the ARV class of GS-5894 (i.e., NNRTI), will be summarized for each GS-5894 cohort by the Clinical Virology group.

6.2.5. Analysis of Other Efficacy Endpoints

Maximum Reduction in Plasma HIV-1 RNA Postbaseline to Day 11
The maximum postbaseline reduction in plasma HIV-1 RNA (log_{10} copies/mL) from Day 2 through Day 11 will be analyzed using the same statistical methods used for the primary endpoint analysis. Baseline value, lowest post-baseline HIV-1 RNA value from Day 2 to Day 11, and the lowest change from baseline in HIV-1 RNA (log_{10} copies/mL) from Day 2 to Day 11 for each participant will be summarized by GS-5894 cohort and for the historical placebo group.

Change from Baseline in HIV-1 RNA by Visit
Baseline value, HIV-1 RNA (log_{10} copies/mL), and change from baseline in HIV-1 RNA (log_{10} copies/mL) will be summarized descriptively by visit for each GS-5894 cohort and for the historical placebo control group through Day 11.

Mean ± 95% confidence interval (CI) and median (Q1, Q3) of the change from baseline in HIV-1 RNA (log_{10} copies/mL) at each visit will be plotted through Day 11 using a line plot with a separate line displayed for each GS-5894 cohort and for the historical placebo group. Placebo data will be displayed for participants with a measurement collected in the analysis visit window.

Change from Baseline in CD4 by Visit
Baseline values, values at each postbaseline visit (Day 11, 18, 25, and 39), and the change from baseline in CD4 cell count (/μL) and CD4 percentage by visit will be summarized by GS-5894 cohort.

Percentage of Participants with HIV-1 RNA < 50 copies/mL by Visit from Day 11 to Day 39
The number and percentage of participants with HIV-1 RNA < 50 copies/mL (split into categories "< 20 copies/mL" [with subcategories "< 20 copies/mL Detectable", "< 20 copies/mL Not Detectable"] and "20 to < 50 copies/mL") by visit using the Cobas 6800 assay will be displayed for each GS-5894 cohort and overall using the missing = excluded method at the last visit prior to adding SOC (Day 11) and at visits after adding SOC (Days 18, 25, and 39).

For participants who did not meet the criteria HIV-1 RNA < 50 copies/mL at the visit, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized:

- 50 to < 200 copies/mL
- ≥ 200 copies/mL

Missing data will be excluded in the computation of percentages (i.e., missing data points will be excluded from both numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit. No statistical testing is planned.

All efficacy endpoints will include participants in the FAS.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events were graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. A Grade 5 event indicates death. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AE met the definition of an SAE that was specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date on or after the study drug start date.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by GS-5894 cohort and overall for events with an onset date up to Day 11 (prior to adding SOC) and for the entire study.

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug (only applicable for cohorts that were administered multiple doses)
- TEAEs leading to premature discontinuation of study
- TEAEs leading to death (i.e., outcome of death)

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and GS-5894 cohort (and overall):

- TEAEs, by maximum severity
- TEAEs up to Day 11, by maximum severity
- TEAEs with Grade 3 or higher, by maximum severity

- TE treatment-related AEs, by maximum severity
- TE treatment-related AEs with Grade 3 or higher, by maximum severity
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs and TE treatment-related AEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug or study

7.2. Laboratory Evaluations

Laboratory data collected during the substudy will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include all data collected after the first dose date of study drug unless stated otherwise. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by GS-5894 cohort (and overall) for selected laboratory tests specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3

7.2.2. Graded Laboratory Values

The DAIDS Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed postbaseline will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and GS-5894 cohort (and overall); participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Graded laboratory abnormalities collected up to Study Day 11 (prior to the participant initiating standard of care therapy on Day 11)
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with ≥ 1 nonmissing postbaseline value.

A by-participant listing of treatment-emergent laboratory abnormalities and a listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by participant ID number and visit in chronological order. These listingss will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by GS-5894 cohort (and overall) for body weight, BMI, and vital signs as follows:

- Baseline value
- Value at each postbaseline time point [visit]
- Change from baseline at each postbaseline time point [visit]

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications and Disease-Specific Medications

Prior and concomitant medications (i.e., non-antiretroviral [non-ARV] medications) collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug Dictionary.

Disease-specific medications (i.e., nonstudy drug ARV) used prior to, during, or after the study (if collected) will be coded using the Gilead-modified WHO Drug Dictionary.

7.4.1. Prior and Disease-Specific Prior Medications

Prior and disease-specific prior medications are defined as any medications taken before a participant took their first dose of study drug.

A summary of prior or disease-specific prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken on or after first dose date of study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each GS-5894 cohort (and overall). A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug that continued to be taken after the first dosing date, or medications started after the first dosing date of study drug will be considered to be concomitant medications. Medications started and stopped on the same day as the first dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) on or after the study drug start date will be included in the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) and all nonstudy drug ARV medications will be provided in by-participant listings sorted by participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

Summaries of investigator assessment of ECG readings will be provided for the Safety Analysis Set for each scheduled visit. No formal statistical testing is planned.

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by GS-5894 cohort using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. If all participants have a baseline value then no missing category will be presented at baseline. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

No formal statistical testing is planned.

A by-participant listing for ECG assessment results will be provided by participant ID number and visit in chronological order.

7.6. Other Safety Measures

A by-participant listing of subject pregnancies during the study will be provided by participant ID number. No additional safety measures are specified in the protocol.

Although not necessarily related to safety, a by-participant listing of all comments received during the study on the comments eCRF will be provided by participant ID number, and eCRF form for which the comment applies.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection and Analyses

Intensive PK samples are planned to be collected at several 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 collected for cohorts with more than 1 day of dosing of GS-5894. A single anytime PK collection will occur relative to study drug dosing on Day 1 at each postbaseline visit for all participants (on Days 2, 3, 4, 7, 8, 9, 10, 11, 18, 25, 39, or at early termination [if applicable]). Concentrations of GS-5894 in plasma will be determined using validated bioanalytical assays.

8.1.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

AUC will be calculated by the pharmacologist. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.1.2. PK Parameters

PK parameters will be generated for all participants in the PK Analysis Set. The analyte presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analyte

GS-5894 Cohort	Treatment	Analyte
All GS-5894 Cohorts	GS-5894	GS-5894

The analyte and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The primary PK parameters are [AUC, C_{max}, and C_t] of GS-5894. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
GS-5894	AUC_{last}, AUC_{inf}, AUC_{0-t},%AUC_{exp}, C_{max}, C_{last}, C_t, T_{max}, T_{last}, λ_z, CL/F, $t_{1/2}$, and V_z/F

Individual participant concentration data and individual participant PK parameters for GS-5894 will be listed and summarized using descriptive statistics by GS-5894 cohort. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual participant concentration data by time point and individual participant PK parameters by GS-5894 cohort. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower LOQ for postdose time points. If more than 1/3 of the concentration data for a cohort is BLQ at a PK collection timepoint then the mean, standard deviation, and %CV will not be calculated for that cohort and collection timepoint.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by treatment:

- Individual participant concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics

The following figures may be provided for each analyte by treatment:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)
- Individual participant concentration data versus time (on linear and semlogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LOQ will not be displayed in the figures and remaining points connected. If more than 1/3 of the concentration data for a cohort is BLQ at a PK collection timepoint then the mean and SD will not be calculated (or plotted) for the cohort and collection timepoint.

The following listings will be provided:

- PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age
- Individual data on determination of plasma half-life and corresponding regression correlation coefficient

8.1.3. PK/PD Analyses

Details of the population PK/PD analysis will be provided in a stand-alone population PK/PD analysis plan.

9. REFERENCES

None.

10. SOFTWARE

SAS® Software Version 9.X. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version X.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

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

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**	
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 CCI [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 [of substudy protocol] 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 of the substudy protocol). 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 of the substudy protocol).
p Biktarvy® or Standard of Care 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).

Appendix 2. Details for Statistical Programming

For continuous HIV-1 RNA endpoints change from baseline at Day 11, change from baseline at Day 8, and maximum change from baseline from Day 2 to Day 11, p-values will be presented for each GS-5894 dose cohort vs. placebo.

The following SAS code can be used to get p-values for pairwise comparisons (each GS-5894 cohort vs. placebo) for primary endpoint "change from baseline in HIV-1 RNA (log_{10} copies/mL) at Day 11" and other continuous endpoints:

```
**Assign treatment groups for testing**;
data trtgrp;
      set trtgrp;
         if dose01p='675 mg'  and meal='High-Fat' then trt=1;
    else if dose01p='1200 mg' and meal='Low-Fat'  then trt=2;
    else if dose01p='900 mg'  and meal='High-Fat' then trt=3;
    else if treatment='Placebo'                   then trt=4;
run;

ods output estimates=estimate;
proc mixed data = trtgrp;
class trt ;
model chgD11  = trt / ddfm=kr;

/*least squares means*/
lsmeans trt / diff e;

/* p-values for each GS-5894 trt group and PBO for primary endpoint */
estimate 'cohort 1 vs placebo' trt  1 0 0 -1 / cl alpha=0.05;
estimate 'cohort 2 vs placebo' trt  0 1 0 -1 / cl alpha=0.05;
estimate 'cohort 3 vs placebo' trt  0 0 1 -1 / cl alpha=0.05;
run;
```

Toxicity Grading for Laboratory Values:

DAIDS Toxicity Grading Scale (Version 2.1) is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Appendix 3. Data Collection of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

12.1. Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

12.2. Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table 12-1). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit will be assigned as follows:

i) If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii) If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same participant and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this participant and this visit will be categorized as "Virtual Visit"

iii) Otherwise result is missing

Table 12-1. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits.

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

GS-US-544-5905-01_SAP_15Sep2023

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	16-Sep-2023 00:58:55
PPD	Clinical Development eSigned	19-Sep-2023 23:20:22