STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Study to Evaluate the Efficacy of GS-9131 Functional Monotherapy in HIV-1-Infected Adults Failing a Nucleos(t)ide Reverse Transcriptase Inhibitor-Containing Regimen with Nucleos(t)ide Reverse Transcriptase Inhibitor Resistant Virus
Name of Test Drug:	GS-9131(+Bictegravir+Tenofovir Alafenamide)
Study Number:	GS-US-442-4148
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	Bictegravir, GS-9883, B
BLQ	below limit of quantitation
BMI	body mass index
BSA	body surface area
CD4	cluster determinant 4
CG	Cockcroft-Gault
CI	confidence interval
CRF	case report form
CSR	clinical study report
DOB	date of birth
DOT	directly observed therapy
DP	diphosphate
DNA	Deoxyribonucleic Acid
DRV	darunavir
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eGFR(CG)	estimated glomerular filtration rate using Cockcroft-Gault formula
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
Gilead	Gilead Sciences, Inc.
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ID	identification
IDMC	independent data monitoring committee
INR	international normalized ratio
INSTI	integrase strand-transfer inhibitor
LDL	low density lipoprotein
LLOQ	lower limit of quantitation
LLT	lowest level term

MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
PTM	placebo-to-match
Q	quartile
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
RT	reverse transcriptase
RTV	Ritonavir
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TAF	tenofovir alafenamide
TAM	thymidine analogue mutations
TE	treatment-experienced
TEAE	treatment-emergent AE
TFL	tables, figures, and listings
TFV	tenofovir
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	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)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	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) of the final analysis for Study GS-US-442-4148, which will be performed when all subjects have completed or prematurely discontinued from the study. This SAP is based on the study protocol amendment 3 dated 01 November 2018 and the electronic case report form (eCRF). The SAP will be finalized before data finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the short-term antiviral potency of GS-9131 functional monotherapy compared to placebo-to-match (PTM) GS-9131, each administered once daily with the existing failing antiretroviral (ARV) regimen, as demonstrated by the proportion of subjects achieving human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) > 0.5 $\log_{10}$ decreases from baseline through up to 14 days of therapy.

The secondary objectives of this study are as follows:

Part 1

- To evaluate the efficacy of GS-9131 functional monotherapy as determined by the change from baseline in $\log_{10}$ HIV-1 RNA at Day 11 (Sentinel Cohort 1) or Day 15 (Sentinel Cohort 2 and Randomized Cohort).

Part 2

- To evaluate the safety and efficacy of a regimen containing GS-9131 + bictegravir (BIC) + darunavir (DRV) + ritonavir (RTV) through 24 weeks of treatment in subjects from Sentinel Cohort 1 switched from a failing regimen.

- To evaluate the safety and efficacy of a regimen containing GS-9131 + BIC + tenofovir alafenamide (TAF) through 24 weeks of treatment in subjects from Sentinel Cohort 2 and Randomized Cohort who switched from a failing regimen.

- To characterize the pharmacokinetics (PK) of GS-9131 in treatment-experienced (TE) patients.

- To evaluate the number of subjects with treatment-emergent Nucleos(t)ide Reverse Transcriptase Inhibitor (NRTI), Protease Inhibitor (PI), and Integrase Strand-transfer Inhibitors (INSTI) mutations at the time of virologic failure.

1.2. Study Design

Part 1: GS-9131 Functional Monotherapy

The study will consist of 3 cohorts - 2 Sentinel Cohorts and 1 Randomized Cohort.

Sentinel Cohort 1 will enroll 10 TE viremic HIV-1 subjects to receive open-label GS-9131 60 mg for 10 days in addition to their current failing ARV regimen.

Sentinel Cohort 2 will enroll up to 10 TE viremic HIV-1 subjects to receive open-label GS-9131 180 mg for 14 days in addition to their current failing ARV regimen.

Sentinel cohort subjects who meet criteria for Part 2, will transition to Part 2 and not participate in the randomized portion of this study.

Randomized Cohort: The Sentinel Cohorts will be followed by a Randomized Cohort that is a double-blind comparison of the addition of GS-9131 (up to 180 mg), or PTM to the current failing ARV regimen in viremic HIV-1 positive adults. Randomization and dosing into the Randomized Cohort will begin after review of the clinical data in the second Sentinel Cohort.

In the Randomized Cohort, up to 48 subjects failing their current ARV regimen will be randomized 1:1:1:1 to GS-9131 (up to 3 active dose levels, up to 180 mg), or PTM. The GS-9131 dose for Treatment Arms A-C will be determined following review of the safety, activity and available PK data from Sentinel Cohort 2.

GS-9131 will be added to their failing regimen for 14 days as follows:

Treatment Arms A-C: GS-9131 once daily + current failing antiretroviral therapy (ART) regimen (n 12 per Treatment Arm)

Treatment Arm D: PTM + current failing ART regimen (n 12)

Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL and > 100,000 copies/mL) at screening.

Study medication will be administered by directly observed therapy (DOT).

Part 2: GS-9131 + BIC + DRV + RTV or GS-9131 + BIC + TAF Combination Therapy

GS-9131(60 mg) + BIC (30 mg) + DRV (800 mg) + RTV (100 mg) (Sentinel Cohort 1)

Subjects who successfully complete all study doses in Sentinel Cohort 1 and show a reduction in plasma HIV RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline following functional monotherapy will discontinue their current failing regimen and start an optimized regimen consisting of GS-9131 (60 mg) + BIC + DRV + RTV for at least 24 weeks.

GS-9131(up to 180 mg) + BIC (75 mg) + TAF (25 mg) (Sentinel Cohort 2 and Randomized Cohort)

Subjects who successfully complete all study doses in Sentinel Cohort 2 and Randomized Cohort (A-C), and show a reduction in plasma HIV-1 RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline during functional monotherapy will discontinue their current failing regimen and start an optimized regimen consisting of GS-9131 + BIC + TAF for at least 24 weeks. All Subjects randomized to the placebo arm (Cohort D) will discontinue their current failing regimen and start a regimen consisting of GS-9131(180 mg) + BIC + TAF for at least 24 weeks.

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The GS-9131 dose for the open label extension will be determined following review of Week 12 efficacy and safety data from Part 2.

Key Eligibility Criteria

HIV-1 infected subjects who meet the following criteria:

- Non-pregnant/non-lactating females, ≥ 18 years of age at Screening. Females of childbearing potential (as defined in Protocol Appendix 7) must have a negative serum pregnancy test at Screening and Day 1.
- Subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as defined in Protocol Appendix 7.
- Estimated glomerular filtration rate (eGFR) (Cockcroft-Gault [CG] equation) ≥ 70 mL/min.
- Currently taking a failing ARV regimen that contains 2 NRTIs and an NNRTI.
- HIV-1 RNA ≥ 500 copies/mL at Screening.
- CD4 > 100 cells/μL at Screening.
- Have a screening genotype showing at least the following resistance mutation profile (a local genotype at the Screening visit is acceptable for enrollment upon review by the Sponsor):

  K65R or

  at least 3 thymidine analogue mutations (TAMs); TAMs are defined as: M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R in reverse transcriptase (RT) or

  Q151M

  and at least one primary resistance mutation to an NNRTI

- No prior or current ARV regimens containing INSTI or PI.
- No evidence of chronic viral hepatitis B or C infection. Note: Subjects with positive hepatitis C virus (HCV) antibody and without detectable HCV RNA are permitted to enroll.
- No evidence of active AIDS-related opportunistic infection, including tuberculosis.

Study Periods / Phases

Part 1: 10 days for Sentinel Cohort 1, and 14 days for Sentinel Cohort 2 and Randomized Cohort.

Part 2: At least 24 weeks.

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Schedule of Assessments

At Screening, laboratory analyses (hematology, chemistry, urinalysis, and serum pregnancy test [for females of childbearing potential]), HIV-1 RNA, cluster determinant 4 (CD4) cell count, vital signs, electrocardiogram (ECG), complete physical examination, and eGFR will be performed. HIV-1 protease, reverse transcriptase genotype/phenotype, and hepatitis B virus (HBV) and HCV serologies will be analyzed.

Part 1:

Sentinel Cohort 1 (GS-9131 60 mg plus Current Failing Regimen)

Following Screening and Day 1 (baseline) visits, subjects will be required to visit the clinic daily on Days 2-11. All study medication will be delivered by DOT on Days 1-10.

Laboratory analyses (hematology, chemistry, and urinalysis) will be performed at Day 1 (baseline), Day 7, and Day 11. A fasting metabolic profile will be performed on Day 1. Urine and serum pregnancy test (females of childbearing potential only) will be done at Screening and Day 1 and a urine pregnancy test on Day 11; positive urine pregnancy test on Day 11 will be confirmed with a serum pregnancy test. CD4 T cell count will be performed at Screening, Day 1 (baseline), and Day 11. A plasma sample for phenotypic and genotypic testing of HIV-1 resistance will be collected at Screening, Day 1, and Day 11. A complete physical examination will be performed at Screening, Day 1 (baseline), and Day 11. Symptom driven physical exam will be performed on Day 2 and Day 7. ECGs will be performed at Screening, Day 1, and Day 11.

On Day 10, all subjects will participate in a PK evaluation.

Samples for HIV-1 RNA will be collected at Screening, Day 1 (baseline), and Days 2, 3, 7, 10, and 11.

Assessments of adverse events (AEs) and concomitant medications will be performed at each visit.

Sentinel Cohort 2 (GS-9131 180 mg plus Current Failing Regimen) and Randomized Cohort (GS-9131 or PTM plus Current Failing Regimen)

Following Screening and Day 1 (baseline) visits, all study medication will be delivered by DOT on Days 1-14.

Laboratory analyses (hematology, chemistry, and urinalysis) will be performed at Days 1 (baseline), 3, 5, 7, 10, 14, and 15. A fasting metabolic profile will be performed on Day 1. Urine and serum pregnancy test (females of childbearing potential only) will be done at Screening and Day 1 and a urine pregnancy test on Days 10 and 14; positive urine pregnancy test will be confirmed with a serum pregnancy test. CD4 T cell count will be performed at Screening and Days 1 (baseline), 10, 14, and 15. A plasma sample for phenotypic and genotypic testing of HIV-1 resistance will be collected at Screening and Days 1, 10, 14, and 15. A whole blood sample for genotypic testing of HIV-1 resistance will be collected at Day 1. A complete physical examination will be performed at Screening and Days 1 (baseline), and 14. Symptom driven physical exam will be performed on Days 2 and 7. ECGs will be performed at Screening, Day 1 and Day 15.

On Day 14, all subjects will participate in a PK evaluation.

Samples for HIV-1 RNA will be collected at Screening and Days 1 (baseline), 3, 7, 10, 14, and 15.

Assessments of AEs and concomitant medications will be performed at each visit.

Part 2:

GS-9131 + BIC + DRV + RTV Regimen (Sentinel Cohort 1)

Subjects in Sentinel Cohort 1 who had a > 0.5 $\log_{10}$ decline in HIV-1 RNA will discontinue their current failing regimen and begin treatment with GS-9131 + BIC + DRV + RTV once daily for 24 weeks. Subjects in Sentinel Cohort 1 who had a ≤ 0.5 $\log_{10}$ decline in HIV-1 RNA are not eligible to continue onto Part 2 and will be discontinued from the study.

At their Day 1 visit for Part 2, AEs, concomitant medications, drug accountability, vital signs, physical examinations, HIV-1 RNA, estimated GFR, hematology, chemistry, CD4 cell count, and urinalysis will be performed.

All subjects will be required to visit the clinic on Day 1, and Weeks 1, 2, 4, 8, 12, 18, and 24. At each visit, AEs, concomitant medications, drug accountability, hematology, chemistry, HIV-1 RNA, CD4 cell count, vital signs, and estimated GFR will be evaluated. A fasting metabolic profile will be performed on Day 1, Week 12 and 24 visits. A complete physical examination will be done at Day 1, Week 12 and 24 visits. A symptom directed physical examination will be done at all other visits. Urinalysis will be performed at Day 1, and Week 4, 12, and 24 visits.

Urine pregnancy test (females of childbearing potential only) will be done on Day 1, and Weeks 4, 8, 12, 18, and 24; positive urine pregnancy test will be confirmed with a serum pregnancy test.

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GS-9131 + BIC + TAF (Sentinel Cohort 2 and Randomized Cohort)

Subjects in the Sentinel Cohort 2 or Randomized Cohort (A-C) who had a > 0.5 $\log_{10}$ decline in HIV-1 RNA in Part 1 will discontinue their current failing regimen and begin treatment with GS-9131 + BIC + TAF once daily for 24 weeks. Subjects who had a ≤ 0.5 $\log_{10}$ decline in HIV-1 RNA are not eligible to continue onto Part 2 and will be discontinued from the study. Subjects in Randomized Cohort D will begin treatment with GS-9131(180 mg) + BIC (75 mg) + TAF (25 mg) once daily for 24 weeks after successful completion of Part 1.

At their Day 1 visit for Part 2, AEs, concomitant medications, drug accountability, vital signs, physical examinations, HIV-1 RNA, estimated GFR, hematology, chemistry, CD4 cell count, and urinalysis will be performed.

All subjects will be required to visit the clinic on Day 1, and Weeks 1, 2, 4, 8, 12, 18, and 24. At each visit, AEs, concomitant medications, drug accountability, hematology, chemistry, HIV-1 RNA, CD4 cell count, vital signs, and estimated GFR will be evaluated. A fasting metabolic profile will be performed on Day 1, Week 12 and 24 visits. A complete physical examination will be done at Day 1, Week 12 and 24 visits. A symptom directed physical examination will be done at all other visits. Urinalysis will be performed at Day 1, and Week 4, 12, and 24 visits. Urine pregnancy test (females of childbearing potential only) will be done on Day 1, and Weeks 4, 8, 12, 18, and 24; positive urine pregnancy test will be confirmed with a serum pregnancy test.

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Pharmacokinetics

Sentinel Cohort 1 (60 mg): Intensive plasma and PBMC samples will be collected in all subjects on Day 10. Serial blood samples for plasma and peripheral blood mononuclear cell (PBMC) PK assessments will be collected at the following timepoints:

Plasma collection on Day 10: Predose (< 5 minutes prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post dose.

PBMC collection on Day 10: Predose (< 5 minutes prior to dosing), 1, 2, 6, and 24 hours post dose.

Sentinel Cohort 2 (180 mg) and Randomized Cohort: Intensive plasma and PBMC PK samples will be collected in all subjects on Day 14. Serial blood samples for plasma and PBMC PK assessments will be collected at the following timepoints:

Plasma collection on Day 14: Predose (< 5 minutes prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post dose.

PBMC collection on Day 14: Predose (< 5 minutes prior to dosing), 1, 2, 6, and 24 hours post dose.

The PK of GS-9131 and its metabolite, GS-9148, in plasma, will be evaluated. The PK of GS-9148-diphosphate (DP) in PBMCs and the PK of other analytes may be explored.

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Randomization

In the Randomized cohort, up to 48 subjects failing their current ARV regimen will be randomized 1:1:1:1 to GS-9131 (up to three active dose levels, up to 180 mg), or PTM.

1.3. Sample Size and Power

For the sample size and power calculation for the randomized cohort in Part 1, assuming that 70% of subjects in each GS-9131 treatment group and 8.3% in the placebo group achieve $> 0.5 \log_{10}$ HIV-1 RNA decrease from baseline at Day 15, a sample size of 12 subjects per treatment group (48 in total) provides 85% power to detect the difference in the response rates between at least one GS-9131 treatment group and placebo group with a Fisher's exact test to be done at a two-sided alpha level of 0.05.

Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

2. TYPE OF PLANNED ANALYSIS

2.1. Day 15 Analysis

The Day 15 analysis will be conducted after all subjects in Part 1 (including the sentinel cohorts and the randomized cohort) either complete their 15-day treatment on GS-9131 or PTM in Part 1 or prematurely discontinued the study drug in Part 1.

2.2. Data Monitoring Committee Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The Week 12 DMC analysis will be conducted after approximately 50% of subjects enrolled in Part 2 complete their Week 12 visit of the study. The purpose of this interim analysis is to provide the DMC with a statistical report for review. More details are documented in the DMC charter.

Gilead does not have a prior intent to ask the DMC to review Week 24 result or consider early termination of the study even if there is early evidence of favorable efficacy.

2.3. Week 24 Interim Analysis

The Week 24 interim analysis will be conducted after all subjects either complete their Week 24 visit or prematurely discontinue from the study drug.

2.4. Final Analysis

The final statistical analysis will be conducted after all subjects either complete the study or prematurely discontinue from the study.

The study was discontinued according to the pre-defined criteria: Study GS-US-442-4148 will be stopped if 50% or more of the subjects enrolled in the Sentinel Cohort 2 fail to achieve > 0.5 log10 reduction in plasma HIV RNA from baseline after 14 days of GS-9131 functional monotherapy. Therefore, no interim analyses have been performed. This SAP describes the final analysis.

All data collected in Part 1 up to the first dose date of Part 2 (if available) will be included in the tables, figures and listings. Data collected in Part 2 will only be include in listings (unless specified otherwise), considering the small sample size in Part 2 (4 subjects).

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject. The treatment group to which subjects are enrolled will be used in the listings.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before data finalization. The analysis set will be identified and included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by cohort.

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

3.1.1. All Enrolled Analysis Set

The **All Enrolled Analysis Set** includes all subjects who received a study subject identification number in the study after screening. This is the primary analysis set for by-subject listings.

3.1.2. Safety Analysis Set

The **Safety Analysis Set** includes all subjects who took at least 1 dose of study medication. Both safety and efficacy data will be analyzed using this analysis set for subjects enrolled in Part 1 Sentinel Cohorts.

3.1.3. Pharmacokinetic Analysis Set

The **PK Analysis Set** includes all subjects who (1) are enrolled into the study, (2) have received at least 1 dose of active drug, and (3) have at least 1 nonmissing plasma PK concentration data for any analyte of interest reported by the PK lab. The PK analysis set will be used for general PK analyses.

3.1.4. PBMC PK Analysis Set

The **PBMC PK Analysis Set** will include all subjects who (1) are enrolled into the study, (2) have received at least 1 dose of active drug, and (3) have at least 1 nonmissing PBMC PK concentration data for GS-9148-DP. The PBMC PK Analysis Set will be used for PBMC PK analyses of GS-9148-DP.

3.2. Subject Grouping

Subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

There is no stratification for analysis.

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for this analysis.

3.5. Multiple Comparisons

No multiplicity adjustments will be applied.

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 done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

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 (in years) on the date of the first dose of study drug will be used for analyses and presented in listings. If age on first dose date of study drug is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject 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.

Laboratory data (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 LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the 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 LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The 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 LOQ).

Logarithm (base 10) transformation will be applied to HIV-1 RNA data for efficacy analysis. HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purpose.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples. Concentration values that are below limit of quantitation (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 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects 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 subjects 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 subjects 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 subjects 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 Windows

3.8.1. Definition of Predose, Postdose, and Study Day for Part 1

Predose value is defined as the last available off-treatment value collected prior to the first dose of GS-9131 in Part 1 Sentinel cohorts.

Postdose value is defined as any value collected after the first dose of GS-9131 up to the date of the last dose of GS-9131 in Part 1 plus 30 days, and before the first dose date of Part 2 if applicable.

Study Day will be calculated from the first dosing date of GS-9131 in Part 1 Sentinel cohorts as follows:

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

Study day 1 is the day of first dose of GS-9131 administration in Part 1 Sentinel cohorts.

3.8.2. Analysis Visit Windows for Part 1

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in summaries. However, the following exceptions will be made:

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of predose value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- For subjects who discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as “Early Termination Visit”.

Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

The nominal visits for HIV-1 RNA, laboratory tests and vital signs, CD4 cell count and ECG are summarized in Table 3-1, Table 3-2, and Table 3-3 respectively.

Table 3-1. Predose and Postdose Visits for HIV-1 RNA

Cohort	Visit Label
Sentinel Cohort 1	Predose
	Treatment Day 2
	Treatment Day 3
	Treatment Day 7
	Treatment Day 10
	Treatment Day 11
Sentinel Cohort 2	Predose
	Treatment Day 3
	Treatment Day 7
	Treatment Day 10
	Treatment Day 14
	Treatment Day 15

Table 3-2. Predose and Postdose Visits for Laboratory Tests (Hematology, Chemistry, and Urinalysis), and Vital Signs

Cohort	Visit Label
Sentinel Cohort 1	Predose
	Treatment Day 7
	Treatment Day 11
Sentinel Cohort 2	Predose
	Treatment Day 3
	Treatment Day 5
	Treatment Day 7
	Treatment Day 10
	Treatment Day 14
	Treatment Day 15

Note: Vital signs for Sentinel Cohort 2 will not be summarized on Day 5 and Day 15, since they were not collected on these days.

Table 3-3. Predose and Postdose Visits for CD4 Cell Count and ECG

Cohort	Visit Label
Sentinel Cohort 1	Predose
	Treatment Day 11
Sentinel Cohort 2	Predose
	Treatment Day 10
	Treatment Day 14
	Treatment Day 15

Note: ECG for Sentinel Cohort 2 will not be summarized on Day 14, since they were not collected on these days.

3.8.3. Selection of Data in the Event of Multiple Records on the Same Day

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

If multiple valid, nonmissing observations exist on a day, records will be chosen based on the following rules if a single value is needed:

- For predose and postdose HIV-1 RNA, the latest (considering both collection date and time) record(s) on the scheduled visit will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (ie, 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 "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

- For predose of other assessments, the last available non-missing record on or prior to the date and time of 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 predose value will be the average (arithmetic or geometric mean, as appropriate) of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety ECG findings) for categorical data.

- For postdose of other assessments, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by cohort for each country or investigator within a country and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided by cohort. This summary will include the number of subjects screened, screen failure subjects who were not enrolled, subjects who met all eligibility criteria and were not enrolled, subjects enrolled, and subjects in the Safety Analysis Set.

In addition, the number and percentage of the subjects in the following categories will be summarized:

- Completed study drug in Part 1 Sentinel cohorts
- Did not complete study drug with reason for premature discontinuation of study drug in Part 1
- Entered into Part 2
- Completed study drug in Part 2
- Did not complete study drug with reason for premature discontinuation of study drug in Part 2
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

In addition, the total number of subjects who were enrolled, and the number of subjects in each of the disposition categories listed above will be displayed in a flowchart.

Recommended sentence to add for all randomized studies:

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

- Reasons for premature study drug or study discontinuation

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

A subject's extent of exposure to study drug data will be generated from the study drug administration page in the eCRF. Exposure data will be listed.

4.3. Protocol Deviations

A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. Any deviations identified will be evaluated to determine if it justifies excluding the subject from any analysis sets.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m2]) will be summarized by cohort using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- HIV-1 RNA (copies/mL)
- CD4+ cell count (/μL)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)

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

5.3. Medical History

General medical history data will be collected at screening and listed only.

A by-subject listing of general medical history will be provided by subject ID number in ascending order. The listing will include relevant medical condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

6. EFFICACY ANALYSES

Since the study was prematurely discontinued, there was no efficacy data from the randomized cohort. The efficacy analysis will only include the efficacy data from the sentinel cohorts.

Predose and change from Predose in log10 HIV-1 RNA, CD4 cell count, and CD4% will be summarized by visit and cohort for Part 1.

All efficacy data including HIV-1 RNA, CD4 cell count, and CD4 % from the entire study including Part 2 will be listed.

7. SAFETY ANALYSES

Safety data from the Sentinel Cohorts of the study in Part 1 will be summarized for the subjects in the Safety Analysis Set. All safety data collected up to 30 days after the Part 1 Sentinel Cohorts last dose date and before the Part 2 first dose date (if applicable) will be summarized by cohort, unless specified otherwise. All safety data from both Parts of the study will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory 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 lowest-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be left as "missing" data listings.

7.1.3. Relationship of Adverse Events to Study Drug

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-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before database 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 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug.
- Any AEs leading to premature discontinuation of study drug.

The TEAE definitions will be applied to Part 1 only. AEs onset date will be compared with the Part 1 first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation during Part 1. An AE meeting the TEAE criteria will be considered as a TEAE in Part 1. All AE data including Part 2 will be listed.

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, 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 both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the date of first dose of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the minimum of (1) 30 days after the date of the Part 1 last dose of study drug and (2) Part 2 first dose date if applicable.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the date of the Part 1 first dose 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 Death

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

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by cohort in Part 1. All treatment-emergent deaths observed in the study will also be included in this summary. The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and cohort as follows:

- TEAEs

- Grade 2, 3, or 4 TEAEs
- Grade 3 or 4 TEAEs
- Treatment-emergent study drug-related AEs
- Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- Grade 3 or 4 treatment-emergent study drug-related AEs
- Treatment-emergent SAEs
- Treatment-emergent study drug-related SAEs
- TEAEs leading to premature discontinuation from study drug

Multiple events will be counted only once per subject 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 subject during the study.

In addition to the above summary tables, all TEAEs, Grade 3 or 4 TEAEs, treatment-emergent study drug-related AEs, Grade 2, 3, or 4 treatment-emergent study drug-related AEs, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings for all AEs regardless of Part will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study-Drug-Related SAEs
- Deaths report
- AEs leading to premature discontinuation of study drug

7.2. Laboratory Evaluations

Laboratory data collected during Part 1 of the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set. 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 imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately for all data collected from both Parts of the study. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead 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 Cohort (different dose of GS-9131) for each laboratory test specified in the study protocol as follows:

- Predose values
- Values at each postdose time point
- Change from predose at each postdose timepoint

Predose and postdose values will be defined as described in Section 3.8.1. Change from predose to a postdose visit will be defined as the visit value minus the predose value. Laboratory test results collected at unscheduled visits will be included for the predose and postdose maximum and minimum value selection. 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 Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning 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 (ie, increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (eg, grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be grade 0, except for lipid tests.

For triglycerides, LDL, and cholesterol, protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

7.2.2.1. Treatment Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from predose at any posedose time point, up to 30 days after Part 1 last dose date or before Part 2 first dose date (if applicable), whichever occurs earlier. If the relevant predose laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol.

Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Maximum postdose grade, instead of treatment-emergent grade, for nonfasting glucose (including glucose results without a known fasting status) will be summarized, as nonfasting glucose was not assessed at predose visit for most of the subjects; therefore, an abnormality is treatment-emergent or not cannot be determined for these subjects.

Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on dipstick, labeled as Hematuria (Dipstick), are assessed routinely and assigned a toxicity grade in this study. Urine RBC based on microscopic examination will be presented in laboratory toxicity summary tables and listings while urine blood based on dipstick will be presented in the listings only.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at predose and each scheduled postdose time point.

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

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent Grade 2, 3, and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postdose values up to the minimum of (1) 30 days after Part 1 last dose date, and (2) Part 2 first dose date (if applicable).

A by-subject listing of all treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study (including Part 2) for the lab test of interest, with all applicable severity grade displayed.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by Cohort for vital signs and body weight as follows:

- Predose values
- Values at each postdose time point
- Change from predose at each postdose time point

Predose and postdose values will be defined as described in Section 3.8.1. Change from predose to a postdose visit will be defined as the postdose value minus the predose value. Body weight and vital signs measured at unscheduled visits will be included for the predose value selection.

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-subject listing of vital signs for the entire study (including Part 2) will be provided by subject ID number and visit in chronological order. In the same listing, a by-subject listing of body weight, height, and BMI will be provided.

7.4. Prior and Concomitant Medications

7.4.1. Antiretroviral Medications

Any nonstudy ARV medications used prior to, during, or after the study (if collected) are all recorded on the ARV eCRF. All ARV medications recorded on the ARV eCRF will be coded using the Gilead-modified World Health Organization (WHO) Drug Dictionary for ARV medication. The WHO preferred name and drug code will be attached to the clinical database. All ARV medications recorded on the ARV eCRF will be listed. No inferential statistics will be provided.

7.4.2. Concomitant Non-Antiretroviral Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from Part 1 first dose date to Part 1 last dose date and before Part 2 first dose date, whichever occurs earlier, will be summarized (number and percentage of subjects) by Cohort and preferred name. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted by decreasing order of total frequency.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after Part 1 last dose date
- The month and year of stop of the medication is before Part 1 first dose date

If the start and stop date of non-ARV medications are complete, the start date is not after Part 1 last dose date and the stop date is not before Part 1 first dose date, or the non-ARV medications are marked as ongoing and start date is on or before Part 1 last dose date, the non-ARV medications are concomitant for Part 1 of the study.

Summaries of non-ARV concomitant medications will be provided for the Safety Analysis Set.

Subjects with any non-ARV concomitant medications during the study (including Part 2) will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each visit compared with predose values will be presented by Cohort using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at predose or postdose will not be included in the denominator for percentage calculation. No inferential statistics will be provided.

A by-subject listing for ECG assessment results for the entire study including Part 2 will be provided by subject ID number and visits in chronological order.

7.6. Other Safety Measures

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

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

7.7. Changes from Protocol-Specified Safety Analyses

Due to the early discontinuation of the study, the safety analyses (tables) will be performed for Sentinel Cohorts in Part 1 only. All safety data including Part 2 will be listed.

8. PHARMACOKINETIC ANALYSES

8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic 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 zero.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. 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_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of the 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.

8.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects for whom parameters can be derived. The analyte(s) presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

	Treatment	Analyte(s)
Part 1 Sentinel Cohort 1	GS-9131 (60 mg) tablet + Failing Regimen	GS-9131, GS-9148, GS-9148-DP
Part 1 Sentinel Cohort 2	GS-9131 (180 mg) tablet + Failing Regimen	GS-9131, GS-9148, GS-9148-DP
Part 2 (rollover from Sentinel Cohort 1)	GS-9131 (60 mg) tablet + BIC + DRV + RTV	GS-9131, GS-9148, BIC
Part 2 (rollover from Sentinel Cohort 2)	GS-9131 (180 mg) tablet + BIC + TAF	GS-9131, GS-9148, BIC, TAF, TFV-DP

The PK parameters of each analyte presented in Table 8-2 will be calculated, as appropriate, and summarized by treatment groups. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte

Analyte	Parameters
GS-9131, BIC, TAF	AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CL/F, Vz/F, and $t_{1/2}$
GS-9148	AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}
GS-9148-DP, TFV-DP	AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}

8.3. Statistical Analysis Methods

Individual subject concentration data and individual subject PK parameters for GS-9131 and its metabolite (GS-9148), and GS-9148-DP, TAF, its metabolite TFV-DP, and BIC, as appropriate, will be listed and summarized using descriptive statistics by treatment group. Summary statistics (numbers of subjects, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by treatment group. Moreover, the geometric mean, 95% confidence interval (CI), and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and one-half of the LOQ for postdose time points.

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

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

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics
- Individual subject PBMC PK parameters and summary statistics
  The following figures will be provided for each analyte by treatment group:
- Individual subject concentration data versus time (on linear and semilogarithmic scales)
- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- PK sampling details by subject, 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
- Listing of study drug administration record for PK dosing

There are no statistical comparisons for the PK analysis.

9. REFERENCES

No references in this document.

10. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA) is to be used for all programming of tables, listings, and figures.

nQuery Advisor® Version 6.0 (Statistical Solutions, Cork, Ireland) is to be used for sample size and power calculation.

Phoenix WinNonlin® Version 6.4 (Certara USA Inc., Princeton, NJ, USA) is to be used for all PK analyses.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Study Procedures Table – Cohort 1

		Part 1 (Sentinel Cohort 1 Randomized)[c] Days											Part 2 Weeks[e,j] (+/- 4 days)								CCI		
Study Procedures	**Screening[a,b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[d]**	**Day 1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**	**Every 12 Weeks**	**30 Day Follow-up[c]**	**ESDD[h]**
Informed Consent	X																						
Medical History	X																						
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X
Complete Physical Exam	X	X										X	X					X		X			X
Symptom Directed Physical Exam			X					X						X	X	X	X		X		X	X[i]	
12 Lead ECG (performed supine)	X	X										X	X							X		X	
Height	X																						
Vital Signs and Weight	X	X						X				X	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile	X	X						X				X	X	X	X	X	X	X	X	X	X	X[i]	X
Chemistry Profile	X	X						X				X	X	X	X	X	X	X	X	X	X	X[i]	X
Urinalysis	X	X						X				X	X			X		X		X	X	X[i]	X
Metabolic Profile[k]		X											X					X[k]		X[k]	X		
Estimated Glomerular Filtration Rate	X											X	X	X	X	X	X	X	X	X	X	X[i]	X
Serum Pregnancy Test[l]	X	X																					
Urine Pregnancy Test[l]	X	X										X	X			X	X	X	X	X	X	X	X
FSH Testing[v]	X																						
Plasma, Serum, CCI Storage Sample		X										X	X			X	X	X	X	X	X	X	X
HCV Serology[m]	X																			X			
HBV blood panel	X												X							X	X		
Plasma HIV 1 RNA	X	X	X	X				X			X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Screening[a,b]	Part 1 (Sentinel Cohort 1 Randomized)[c] Days											Part 2 Weeks[e,j] (+/- 4 days)								CCI		
		1	2	3	4	5	6	7	8	9	10	11[d]	Day 1	1	2	4	8	12	18	24	Every 12 Weeks	30 Day Follow-up[c]	ESDD[h]
CD4 Cell Count	X	X										X	X	X	X	X	X	X	X	X	X	X	X
HIV 1 Genotype/ Phenotype[j]	X	X										X											X
Timed PK Sample[n]																X		X	X				
Single Anytime PK Sample[o]															X		X			X			
CCI																							
Intensive PK Sampling[p]											X					X[c]	X[c]						
PBMC Sampling[r]											X												
Randomization[s]		X																					
Collect Subject Dosing Diary to Subjects												X				X	X	X	X	X	X		X
In clinic Dosing[t]		X	X	X	X	X	X	X	X	X	X												
Study Drug Dispensation[u]													X	X	X	X	X	X	X	X	X		
Drug Accountability													X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Part 1 Day 1 visit. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor

b Results from the screening genotype report and confirmed eligibility must be obtained before proceeding with Day 1 Visit. Local genotype at the Screening Visit is acceptable for enrollment upon review by the Sponsor. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor if the genotype results are delayed.

c Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 10 safety, efficacy and available PK data from the 10 subjects in the Sentinel Cohort are reviewed.

d Before proceeding into Part 2, subjects who have completed Day 10 of Part 1 (from either the Sentinel or Randomized Cohorts) will discontinue GS 9131 or PTM but remain on their failing regimen until the site is notified of the subject's eligibility to proceed to Part 2**.** This period shall be no longer than 14 days while awaiting Day 10 HIV 1 RNA results and the authorization to proceed from Gilead. Once notified of their eligibility into Part 2 of the study, the subject will discontinue their failing regimen before initiating any Part 2 Day 1 study procedures. In the event the plasma HIV 1 RNA test results performed by the central laboratory are delayed beyond 14 days, a subject may still proceed to Part 2 of the study if the test results from the local laboratory show a reduction in plasma HIV 1 RNA > 0.5 $\log_{10}$ compared to pre GS 9131 baseline after 10 days of GS 9131 functional monotherapy in Part 1 of the study.

e All study visits are to be scheduled relative to the Part 2 Day 1 visit date. Visit windows are ± 4 days of the protocol specified date through Week 8, ± 4 days of the protocol specified date through Week 24, CCI .

[redacted]

h ESDD visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 24 visit even as the subject discontinues study drug.

i Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

j HIV 1 genotype/phenotype testing for subjects with confirmed virologic failure and HIV 1 RNA >200 copies/mL, at early study discontinuation or Week 24. Following virologic rebound, subjects will be asked to return to the clinic (1 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV 1 RNA and HIV 1 genotype/phenotype (reverse transcriptase, protease, and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema.

k Collected fasted (no food or drinks, except water, at least 8 hours prior to blood collection) only at Part 2 Day 1, Week 12, and Week 24. Collected non fasted at all other visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the assessments.

l Females of childbearing potential only. Urine and serum pregnancy test will be done at Screening and Day 1. If the urine and serum test is positive at screening, the subject will not be enrolled. A positive urine pregnancy test at any visit will be confirmed with a serum test. If the test is positive the subject will be discontinued from the study.

m Hepatitis C Virus (HCFAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

n Timed PK Sample: collected at predose and one within 15 minutes 4 hours post dose **(Part 2 Weeks 4, 12 and 18)**

o Single Anytime PK Sample: collected without regard to time of dosing **(Part 2 Weeks 2, 8 and 24)**

p Intensive PK samples will be collected on Part 1 Day 10**.** Prior to the administration of study drug, a predose (<5 minutes prior to dosing) blood sample will be collected. **Subjects will then take an observed dose of study drug at the clinic.** Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hour post dose.

[redacted]

r PBMC collection on Day 10: Predose (<5 minutes prior to dosing), 1, 2, 6 and 24 hours post dose.

s Randomization may be performed up to 3 days prior to the in clinic Day 1 visit provided that all screening procedures have been completed, and subject eligibility has been confirmed.

t All study medication in Part 1 will be delivered by directly observed therapy on Days 1 10.

u Subjects must be reminded to take study drug at the same time each day except on days with Timed PK sample and Intensive PK.

v For female subject post menopausal for less than two years, if FSH <40 mIU/ mL a serum pregnancy test will be required

Appendix 2. Study Procedures Table – Sentinel Cohort 2/Randomized Cohort Part 1

Study Procedures/Sentinel Cohort 2/Randomized Cohort Part 1	Screening[a,b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed Consent	X															
Medical History	X															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X													X	X
Symptom-Directed Physical Exam			X					X			X					
12-Lead ECG (performed supine)	X	X									X					X
Height	X															
Vital Signs and Weight	X	X		X				X			X				X	
Hematology Profile	X	X		X		X		X			X				X	X
Chemistry Profile	X	X		X		X		X			X				X	X
Urinalysis	X	X		X		X		X			X				X	X
Metabolic Profile[k]		X														
Estimated Glomerular Filtration Rate	X	X		X		X			X			X			X	
Serum Pregnancy Test[l]	X	X														
Urine Pregnancy Test[l]	X	X									X				X	
FSH Testing[v]	X															
Plasma, Serum, CCI Storage Sample		X		X		X		X			X	X			X	X
HCV Serology[m]	X															
HBV blood panel	X															
Plasma HIV-1 RNA	X	X		X				X			X				X	X
CD4+ Cell Count	X	X									X				X	X

Study Procedures/Sentinel Cohort 2/Randomized Cohort Part 1	**Screening[a,b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
HIV-1 Genotype/ Phenotype[j]	X	X									X				X	X
Whole blood sample for genotypic testing		X														
CCI																
Intensive PK Sampling[p]															X	
PBMC Sampling[r]															X	
Randomization[s]		X														
Collect Subject Dosing Diary to Subjects																X
In-clinic Dosing[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Part 2 Weeks[e,j] (+/- 4 days)								CCI	**30 Day Follow-up[g]**	**ESDD[h]**
Study Procedures	**Day1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**	**Every 12 Weeks**		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X[i]	X
Complete Physical Exam	X					X		X			X
Symptom-Directed Physical Exam		X	X	X	X		X		X	X[i]	
12-Lead ECG (performed supine)	X							X		X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile	X	X	X	X	X	X	X	X	X	X[i]	X

	Part 2 Weeks[e,j] (+/- 4 days)								CCI	30 Day Follow-up	ESDD[h]
Study Procedures	**Day1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**	**Every 12 Weeks**		
Chemistry Profile	X	X	X	X	X	X	X	X	X	X[i]	X
Urinalysis	X			X		X		X	X	X[i]	X
Metabolic Profile[k]	X					X[k]		X[k]	X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X[i]	X
Serum Pregnancy Test[l]											
Urine Pregnancy Test[l]	X			X	X	X	X	X	X	X	X
Plasma, Serum, CCI Storage Sample	X			X	X	X	X	X	X	X	X
HCV Serology[m]								X			
HBV blood panel	X							X	X		
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Genotype/ Phenotype[j]											X
Timed PK Sample[n]				X		X	X				
Single Anytime PK Sample[o]			X		X			X			
Intensive PK Sampling & PBMC Sampling[p]				X	X						
Collect Subject Dosing Diary to Subjects				X	X	X	X	X	X		X
Study Drug Dispensation[u]	X	X	X	X	X	X	X	X	X		
Drug Accountability	X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Part 1 Day 1 visit. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor

b Results from the screening genotype report and confirmed eligibility must be obtained before proceeding with Day 1 Visit. Local genotype at the Screening Visit is acceptable for enrollment upon review by the Sponsor. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor if the genotype results are delayed.

c Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 15 safety, efficacy and available PK data from the 10 subjects in the Sentinel Cohort 2 are reviewed.

d Before proceeding into Part 2, subjects who have completed Day 14 of Part 1 (from either the Sentinel or Randomized Cohorts) will discontinue GS 9131 or PTM but remain on their failing regimen until the site is notified of the subject's eligibility to proceed to Part 2**.** This period shall be no longer than 9 days while awaiting HIV 1 RNA results and the authorization to proceed from Gilead. Once notified of their eligibility into Part 2 of the study, the subject will discontinue their failing regimen before initiating any Part 2 Day 1 study procedures. In the event the plasma HIV 1 RNA test results performed by the central laboratory are delayed, beyond 9 days, a subject may still proceed to Part 2 of the study if the test results from the local laboratory show a reduction in plasma HIV 1 RNA > 0.5 $\log_{10}$ compared to pre GS 9131 baseline during the 14 days of GS 9131 functional monotherapy in Part 1 of the study.

e All study visits are to be scheduled relative to the Part 2 Day 1 visit date. Visit windows are ± 4 days of the protocol specified date through Week 24, CCI

[redacted]

h ESDD visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 24 visit even as the subject discontinues study drug.

i Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

j HIV 1 genotype/phenotype testing for subjects with confirmed virologic failure and HIV 1 RNA >200 copies/mL, at early study discontinuation or Week 24. Following virologic rebound, subjects will be asked to return to the clinic (1 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV 1 RNA and HIV 1 genotype/phenotype (reverse transcriptase, protease, and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Protocol Section 6.10).

k Collected fasted (no food or drinks, except water, at least 8 hours prior to blood collection) only at Part 1 Day 1, Part 2 Day 1, Week 12, and Week 24, CCI [redacted]. Collected non fasted at all other visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the assessments.

l Females of childbearing potential only. Urine and serum pregnancy test will be done at Screening and Day 1and a urine pregnancy test on Days 10 and14. If the urine and serum test is positive at screening, the subject will not be enrolled. A positive urine pregnancy test at any visit will be confirmed with a serum test. If the test is positive the subject will be discontinued from the study.

m Hepatitis C Virus (HCFAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

n Timed PK Sample: collected at predose and one within 15 minutes 4 hours post dose **(Part 2 Weeks 4, 12 and 18)**

o Single Anytime PK Sample: collected without regard to time of dosing **(Part 2 Weeks 2, 8 and 24)**

p Intensive PK samples will be collected on Part 1 Day 10 for Sentinel Cohort 1 and Day 14 for Sentinel Cohort 2 and Randomized Cohort**.** Prior to the administration of study drug, a predose (<5 minutes prior to dosing) blood sample will be collected. **Subjects will then take an observed dose of study drug at the clinic.** Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hour post dose.

[redacted]

r PBMC collection on Day 10 for Sentinel Cohort 1 and Day 14 for Sentinel Cohort 2 and Randomized Cohort: Predose (<5 minutes prior to dosing), 1, 2, 6 and 24 hours post dose.
s Randomization may be performed up to 3 days prior to the in clinic Day 1 visit provided that all screening procedures have been completed, and subject eligibility has been confirmed.
t All study medication in Part 1 will be delivered by directly observed therapy on Days 1 14.
u Subjects must be reminded to take study drug at the same time each day except on days with Timed PK sample and Intensive PK.
v For female subject post menopausal for less than two years, if FSH <40 mIU/ mL a serum pregnancy test will be required

Appendix 3. Programming Specification

1. AGE calculated as follows:

   a. AGE (years) is calculated from the number of days between the date of birth (DOB) and Day 1 (Sentinel Cohorts first dose date),

   b. Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c. Divide the result in (b) by 12,

   d. AGE the integer of the result in (c),

   e. If the DOB and Sentinel Cohorts first dose date have the month in common and the birthday is later in the month than the date of Sentinel Cohorts first dose date, then subtract one from the AGE result above.

2. All screened subjects refer to all subjects who are screened (ie, with nonmissing screening date) and have a screening number. For summaries, the same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used to identify unique screened subjects.

3. Screen failure subjects are the subjects who are screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

4. In disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

5. Body mass index and Body Surface Area (BSA)

   BMI and BSA will be calculated only at Part 1 sentinel cohorts predose as follows:

   - BMI (weight [kg])/ (height [meters]^2)
   - BSA (m^2) SQRT([Height(cm) x Weight(kg)]/ 3600)

   Predose height and weight in the Sentinel cohorts Part 1 of the study will be used for this calculation.

6. Toxicity Grades:

   1) For toxicity grade summaries, include all postdose graded results up to 30 days after the Part 1 Sentinel cohorts last dose of study drug, and before Part 2 first dose date (if applicable), not just those used in by-visit summaries.

2) For glucose grading, as specified in SAP Section 7.2.2.1, the treatment-emergent flag cannot be determined for nonfasting glucose (including glucose results without a known fasting status). As a result, these records will be excluded from the "Maximum Treatment-emergent Toxicity Grade" summary in the "Treatment-emergent Laboratory Abnormalities" or "Treatment-emergent Grade 3 or 4 Laboratory Abnormalities" summary tables. In addition, fasting glucose and non-fasting glucose will be listed as two separate laboratory tests in the "Laboratory Abnormalities" and "Grade 3 or 4 Laboratory Abnormalities" listings. Only a maximum postbaseline toxicity flag will be displayed and the treatment-emergent flag will not be displayed for nonfasting glucose as the treatment-emergent flag cannot be determined for nonfasting glucose.

7. Graded Laboratory Abnormalities Summary

The following labels will be used for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	N/A
	Prothrombin Time (PT)	Increase	N/A
Urinalysis	Urine Blood	Increase	N/A
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative)

Note: Prothrombin Intl. Normalized Ratio (INR) and Prothrombin Time (PT) were graded based on the protocol defined toxicity grade scale. The results and toxicity grade will be listed in listing, but not be summarized in lab toxicity summary table.

8. Clarification for “Pharmacokinetic Blood Sampling Time Record” listing

A new variable “Sample age” will be added in this listing, defined as the duration in day between sample collection date and assay date, ie, sample age assay date sample collection date + 1.

SAMTIME (hours) sample collection time (xx:xx) - last dose time before sample collection (xx:xx).

9. Non-study drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Antiviral Medication" listing. Please note that for ARVs recorded on the "Prior ARV" eCRF will NOT be considered as ARVs taken during study. All Prior ARVs with missing end date will be queried to confirm the ARVs were stopped before the Part 1 Sentinel cohort dose date.

10. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purpose. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purpose.

11. PK parameters at the individual subject level should be displayed with the following reported number of decimal places:

    LambdaZ, r2, r2 adj, and CORRXY: 3 decimal places

    $t_{1/2}$, T_{last}, T_{max}, BEGHOUR, and ENDHOUR: 2 decimal places

    AUC_{tau}, $AUC_{0\ last}$, AUC_{inf}, $\%otAUC_{exp}$, Vz/F, CL/F, CLss/F, C_{max}, C_{last} and C_{tau}: 1 decimal place

    NPOINTS: 0 decimal place

    PK concentration data will be reported with 1 decimal place.

SAP_GS-US-442-4148_Final

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	03-Mar-2020 16:13:09
PPD	Biostatistics eSigned	03-Mar-2020 17:06:00