STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination with Other Antiretroviral Agents in People Living with HIV
Name of Test Drug:	Lenacapavir (LEN; GS-6207)
Study Number:	GS-US-200-4334
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Analysis Plan Version:	Version 1.0
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
B/F/TAF	Bictegravir/Emtricitabine/Tenofovir Alafenamide
BIC	Bictegravir
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CSR	clinical study report
DMC	data monitoring committee
DAIDS	Division of AIDS
ECG	electrocardiogram
eCRF	electronic case report form
eGFRCG	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	Full Analysis Set
GLPS	Gilead Global Patient Safety
Hb	hemoglobin
HLT	high-level term
IXRS	interactive web response system
LOQ	limit of quantitation
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PP	per protocol
PT	preferred term
PWH	people with HIV
Q1, Q3	first quartile, third quartile
SAE	serious adverse events
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir diphosphate
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 Week 54 interim analysis for Study GS-US-200-4334, the primary analysis of this study. A formal interim analysis will be performed when all subjects have completed Week 54 assessment or prematurely discontinued from study drug. The purpose of this interim analysis is to support the lenacapavir (LEN; GS-6207) regulatory filing for the indication in the heavily treatment experienced people with HIV (PWH).

This SAP is based on the study protocol amendment 3 dated 01 September 2020 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the Week 54 analysis. 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 efficacy of LEN containing regimens in PWH as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 54

The secondary objectives of this study are as follows:

- To evaluate the efficacy of LEN containing regimens in PWH as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80
- To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80
- To evaluate the safety and tolerability of the LEN containing regimens through 28, 38, 54, and 80 weeks of treatment
- To evaluate the pharmacokinetics (PK) of LEN, bictegravir (BIC), and tenofovir alafenamide (TAF)

1.2. Study Design

Design Configuration and Subject Population

This is a Phase 2, randomized, open label, active controlled, multicenter study.

Approximately 175 treatment-naive PWH who meet all eligibility criteria will be randomized in a 2:2:2:1 ratio to 1 of the following 4 treatment groups. Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Treatment Groups

Treatment Group 1 (n = 50)

Induction: Subjects will receive oral LEN 600 mg, 600 mg, and 300 mg, without regard to food, at Days 1, 2, and 8 respectively. Subjects will also begin oral daily emtricitabine (F)/TAF (200/25 mg), without regard to food from Day 1 onwards for a total of 28 weeks. On Day 15 subjects will receive subcutaneous (SC) LEN 927 mg, without regard to food.

Maintenance: Subjects will receive SC LEN 927 mg at Week 28 and every 26 weeks thereafter. Subjects will discontinue oral daily F/TAF (200/25 mg) at Week 28 and begin taking oral daily TAF (25 mg), without regard to food.

Treatment Group 2 (n = 50)

Induction: Subjects will receive oral LEN 600 mg, 600 mg, and 300 mg, without regard to food at Days 1, 2, and 8 respectively. Subjects will also begin oral daily F/TAF (200/25 mg), without regard to food from Day 1 onward for a total of 28 weeks. On Day 15 subjects will receive SC LEN 927 mg, without regard to food.

Maintenance: Subjects will receive SC LEN 927 mg at Week 28 and every 26 weeks thereafter. Subjects will discontinue oral daily F/TAF (200/25 mg) at Week 28 and begin oral daily BIC (75 mg) without regard to food.

Treatment Group 3 (n = 50)

Subjects will receive oral LEN 600 mg and 600 mg without regard to food at Days 1 and 2, respectively. On Day 3, subjects will begin oral daily LEN 50 mg, without regards to food. Subjects will begin oral daily F/TAF (200/25 mg), without regard to food from Day 1 onwards.

Treatment Group 4 (n = 25)

Subjects will receive oral daily bictegravir/emtricitabine/TAF (B/F/TAF, 50/200/25 mg), without regard to food at Day 1 and throughout their participation in the study.

Key Eligibility Criteria

Treatment naive PWH who meet the following criteria:

- Age ≥ 18 years of age at Screening
- Plasma HIV-1 RNA ≥ 200 copies/mL at Screening
- CD4+ cell count ≥ 200 cells/μL at Screening
- Antiretroviral (ARV) naive with no use of any ARV medications within one month of Screening. Use of pre-exposure prophylaxis (PrEP) (any duration), post-exposure prophylaxis (PEP) (any duration), or HIV-1 treatment (< 10 days therapy total) > 1 month prior to Screening is permitted.

Schedule of Assessments

At screening, laboratory analyses (hematology, chemistry, and urinalysis, and serum pregnancy test [for women]), HIV-1 RNA, CD4+ cell count, vital signs, electrocardiogram (ECG), complete physical examination and estimated glomerular filtration rate (eGFR) will be performed, and hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies will be analyzed. Analysis of the subject's HIV-1 resistance to support eligibility will be completed.

After screening procedures, eligible subjects will be randomized into 1 of the 4 treatment groups in a 2:2:2:1 ratio.

Subjects in Treatment Groups 1, 2, and 3 only, will have visits on Day 1, Day 2, CCI [redacted] Day 8, and Day 15. All subjects will have a Week 4 visit and will continue to attend study visits every 6 weeks until Week 28.

Subjects in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study drug at or prior to Week 28.

After Week 28, subjects will attend study visits on Week 38, Week 54, Week 64, and Week 80. After Week 80, subjects in Treatment Group 4 will complete the study and subjects in Treatment Groups 1, 2, and 3 will be given the option to receive further treatment and continue to attend visits alternating between every 10 weeks and every 16 weeks visits.

At each visit, adverse events (AEs), concomitant medications, laboratory tests, physical examinations, PK, and patient reported outcomes (PROs) will be performed in accordance with the Study Procedures Table.

More details for study procedures could be found in Section 12 (Appendix 1).

Study Duration

Duration of treatment is at least 80 weeks. Subjects in Treatment Group 4 will complete the study at Week 80.

Following successful completion of Week 80 visit, subjects receiving LEN will be given the option to receive further treatment and continue to attend visits on Week 90, Week 106, Week 116, Week 132, Week 142, and will continue to alternate between every 10 weeks and every 16 weeks visits. Subjects willing to continue the study beyond Week 80 in Treatment Groups 1 and 2 will continue to receive SC LEN 927 mg every 6 months (26 weeks) from Week 80 onwards and subjects in Treatment Group 3 will receive oral LEN 50 mg daily from Week 80 until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in the country. Subjects in Treatment Groups 1, 2, and 3 will also receive TAF, F/TAF, or BIC as applicable.

Subjects who discontinue study drugs prior to Week 80 visit or prior to study completion may be required to complete 30-Day, 90-Day and/or 180-Day Follow Up visits after Early Termination Visit.

1.3. Sample Size and Power

A sample size of 50 subjects in Treatment Groups 1 to 3, respectively, was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 54. A total sample size of 75 subjects for each pair of comparisons (ie, between each of the LEN-containing regimen groups [Treatment Groups 1 to 3, n = 50] and the B/F/TAF [Treatment group 4, n = 25]) will provide 39% power to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 54. In this sample size and power calculation, it is assumed a response rate is 90.9% (based on pooled data from Studies GS-US-380-1489 and GS-US-380-1490) for each treatment group and a non-inferiority margin is 0.12.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Data Monitoring Committee Analysis

One external multidisciplinary Data Monitoring Committee (DMC) analysis was conducted after all subjects have completed their Week 16 visit or prematurely discontinued from study drug, all outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis. No formal stopping rules was used by the DMC for safety outcomes. Rather, a clinical assessment was made to determine if the nature, frequency, and severity of AEs associated with a study treatment warrant the early termination of the study in the best interest of the subjects. No alpha penalty will be applied for the primary analysis of the primary efficacy endpoint given that the study is not adequately powered for a formal efficacy evaluation. The purpose of the interim analysis was to provide the DMC with a statistical report for review. More details are documented in the DMC charter.

2.1.2. Week 28 Interim Analysis

The Week 28 interim analysis was conducted after all subjects have completed the Week 28 visit or have prematurely discontinued the study drug, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis. The analysis was used to support the LEN regulatory filing for the indication in the heavily treatment experienced PWH.

2.1.3. Week 80 Interim Analysis

The Week 80 analysis will be conducted after all subjects either complete their Week 80 visit or prematurely discontinue from the study drug, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis.

2.2. Primary Analysis

The Week 54 interim analysis is a planned primary analysis and will be conducted after all subjects have completed Week 54 visit or have prematurely discontinued the study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis.

This SAP describes the analysis plan for the Week 54 interim analysis, the primary analysis of this study.

2.3. Final Analysis

The final analysis will be performed after all subjects have completed the study or have prematurely discontinued the study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

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.

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

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject 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 subject. The treatment group to which subjects were randomized 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 subjects 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 subjects eligible for inclusion will be summarized by treatment group.

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

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study.

This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who were randomized and received at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.3. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set is defined for the primary efficacy analysis. This analysis set includes all subjects in the FAS excluding subjects meeting any of the following criteria:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 54 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation on the study drug completion eCRF page.)
- Subjects who meet the exclusion criterion that was known hypersensitivity to the study drug(s), the metabolites, or formulation excipient.
- Subjects who meet the exclusion criterion for receiving treatment within 3 months prior to screening, or anticipated treatment during the study period with immunosuppressant therapies, hydroxyurea, foscarnet, radiation, or cytotoxic chemotherapeutic agents that listed in Table 5-3 in protocol Section 5.4.
- Nonadherence to once daily (QD) study drug(s): subjects with adherence rate for active once daily study drug(s) up to the Week 54 Visit below the 2.5th percentile

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all subjects who were randomized and received at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

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

CCI [redacted]

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS, subjects will be grouped according to the treatment group to which they were randomized. For all other analyses, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

Subjects will be grouped as follows for table summary:

- Treatment Group 1: SC LEN + (F/TAF → TAF)
- Treatment Group 2: SC LEN + (F/TAF → BIC)
- Treatment Group 3: Oral LEN + F/TAF
- Treatment Group 4: B/F/TAF
- Treatment Groups 1 and 2: SC LEN (for all tables unless specified otherwise)
- Treatment Groups 1, 2 and 3: LEN (for all tables unless specified otherwise)

3.3. Strata and Covariates

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

Efficacy analyses will include HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) at baseline as a stratification factor. The HIV-1 RNA stratum will be reclassified using baseline HIV-1 RNA level for analysis purposes.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following subject subgroups based on FAS:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Baseline HIV-1 RNA (copies/mL): (a) ≤ 100,000 and (b) > 100,000
- Baseline CD4 Cell Count (/uL): (a) < 200 and (b) ≥ 200

3.4.2. Subject Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs (TEAEs) will be analyzed for the following subject subgroups:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made in this Phase 2, non-confirmatory trial.

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.

For missing last dose date of study drug, imputation rules are described in Section 3.8.1. 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

Only year of birth is collected in this study. 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) will be used for analyses and presented in listings. If age at Day 1 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 randomization 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).

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Logarithmic (base 10) transformations 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 purposes.

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 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."

3.8. Analysis Visit Windows

3.8.1. Definition of Key Dates and Study Day

Study Day 1 is defined as the day when the first dose of study drug was taken, as recorded on the Study Drug Administration eCRF. For subjects in Treatment Groups 1-3, the earliest of the first dose dates of any component (ie, LEN or F/TAF) is considered as the first dose date of the study drug.

Last Dose Date is defined as follows for subjects who prematurely discontinued study drug according to Study Drug Completion eCRF.

- For subjects who receive SC injection, the last dose date is defined as the latest nonmissing end date of the study drug used with LEN.
- For subjects who do not receive SC injection, the last dose date is defined as the earliest of the last dose date of any study drug.
- If the date of last dose is incomplete or missing (eg, due to lost to follow-up), the latest nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the dates of any follow-up visits will be used to impute the last dose date.

Study Days are calculated relative to Study Day 1 of study drug and derived as follows:

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

Baseline Value is defined as the last value obtained on or prior to the first dose of study drug.

Last Study Date is the latest nonmissing clinic visit dates, and/or the laboratory visit dates, and/or latest AE onset date and end date, whichever is latest, including the any follow-up visit dates, for subjects who prematurely discontinued study according to the Study Completion eCRF.

Last Exposure Date is defined as follows for subjects who prematurely discontinued study drug according to Study Drug Completion eCRF. This date is defined considering the prolonged exposure of LEN after the last dose date of LEN.

- Treatment Groups 1 and 2:
  - For subjects who receive SC injection, last exposure date is defined as last study date.
  - For subjects who do not receive SC injection, last exposure date is defined as the minimum of the last dose date plus 60 days and the last study date.

- Treatment Group 3: last exposure date is defined as the minimum of the last dose date plus 60 days and the last study date.

- Treatment Group 4: last exposure date is defined as the minimum of the last dose date plus 30 days and the last study date.

3.8.2. Analysis Visit Windows

Subject 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, CD4+ cell count, CD4 %, Hematology, Chemistry, Lipid Panel, Urinalysis, Urine Chemistry, Urine Pregnancy Laboratory Tests, Vital Signs, and Weight are provided in Table 3-1 and Table 3-2 for the LEN-containing regimen groups (Treatment Groups 1-3) and the B/F/TAF group (Treatment Group 4), respectively.

Table 3-1. Analysis Visit Windows for HIV-1 RNA, CD4+ cell count, CD4 %, Hematology, Chemistry, Lipid Panel, Urinalysis, Urine Chemistry, Urine Pregnancy Laboratory Tests, Vital Signs, and Weight for the LEN-containing Regimen Groups (Treatment Groups 1-3)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	≤ 1	1
Day 2	2	2	5
Day 8	8	6	11
Day 15	15	12	21
Week 4	28	22	49
Week 10	70	50	91
Week 16	112	92	133
Week 22	154	134	175
Week 28	196	176	231
Week 38	266	232	322
Week 54	378	323	413
Week 64	448	414	504
Week 80	560	505	595
Week 90	630	596	686
Week 106	742	687	777

Table 3-2. Analysis Visit Windows for HIV-1 RNA, CD4+ cell count, CD4 %, Hematology, Chemistry, Lipid Panel, Urinalysis, Urine Chemistry, Urine Pregnancy Laboratory Tests, Vital Signs, and Weight for the B/F/TAF Group (Treatment Group 4)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	≤ 1	14
Week 4	28	15	49
Week 10	70	50	91
Week 16	112	92	133
Week 22	154	134	175
Week 28	196	176	231
Week 38	266	232	322
Week 54	378	323	413
Week 64	448	414	504
Week 80	560	505	595

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, whereas a time-to-event analysis would not require 1 value per analysis window.

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 date 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 (eg, 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 counts 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 worse 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 "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.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

Key study dates (i.e., first subject screened, first subject randomized, last subject randomized, last subject last visit for the primary endpoint, and last subject last visit for the CSR) will be provided.

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

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the interactive web response system (IXRS) and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided. If there are differences between randomization stratum using screening HIV-1 RNA value and baseline HIV-1 RNA value, a listing of the differences will also be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and total based on all screened subjects. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomized with reasons subjects not randomized, the number of subjects randomized but never dosed (if applicable), the number of subjects randomized, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- Per-Protocol Analysis Set
- Continuing study drug in the main phase
- Completed study drug in the main phase
- Did not complete study drug with reasons for premature discontinuation of study drug in the main phase (if applicable)
- Entering and treated in the extension phase
- Continuing study drug in the extension phase

- Completed study drug in the extension phase
- Did not complete study drug with reasons for premature discontinuation of study drug in the extension phase (if applicable)
- Continuing study
- Completed study
- Did not complete the study with reasons for premature discontinuation of study (if applicable)

Duration of treatment is at least 80 weeks. At Week 80, subjects in Treatment Group 4 will complete the study. Subjects in Treatment Groups 1, 2, and 3 will be given the option to receive further treatment and continue to attend visits beyond Week 80. Main phase data is defined as the data collected on/before Week 80 visit. Extension phase data is defined as the data collected after Week 80 visit.

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

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

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order

4.2. Extent of Study Drug Exposure and Adherence

Study drug administration and study drug dispensing information will be collected in the Study Drug Administration and Study Drug Accountability eCRFs. All data including lot number and kit ID (if applicable) will be listed.

4.2.1. Duration of Exposure to Study Drug

Due to long acting feature of LEN, duration of follow-up to study drug will consider the prolonged exposure of LEN after the last dose date of LEN. Duration of exposure to study drug will be defined as (the last exposure date – the first dose date + 1), and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). Last exposure date is defined in Section 3.8.1 for subjects who prematurely discontinued study drug. For subjects who are still on study drug at the time of the data cut date of the Week 54 analysis, the data cut date will be used to impute the last exposure date.

Duration of exposure will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed and remained through the following time periods: 1 day, 2 days, 8 days, 15 days, 4 weeks (28 days), 10 weeks (70 days), 16 weeks (112 days), 22 weeks (154 days), 28 weeks (196 days), etc. Summaries will be provided based on the Safety Analysis Set. No inferential statistics will be provided.

4.2.2. Adherence to Study Drug

4.2.2.1. Adherence to SC LEN

The adherence to SC LEN will be assessed by adherence to the projected injection interval, which is 26 weeks (182 days) between 2 adjacent injection visits. The number of days from the projected injection visit date will be calculated for each injection visit (excluding the 1st injection visit) as the injection visit date – the previous injection visit date plus 1 day minus 182 days. The number of days from the projected injection visit date will be classified into the following categories:

- < -14 days
- -14 to -8 days
- -7 to -3 days
- ± 2 days
- 3 to 7 days
- 8 to 14 days
- > 14 days

The number and percentage of subjects in each category will be summarized for subjects in Treatment Groups 1 and 2 who receive SC injections for the injection visit of interest.

4.2.2.2. Adherence to Once Daily Study Drug(s)

The adherence to once daily (QD) study drug(s) will be calculated based on 1 study drug for Treatment Groups 1, 2, and 4 (ie, F/TAF up to Week 28 and TAF or BIC from Week 28 onwards for Treatment Groups 1 and 2, and B/F/TAF for Treatment Group 4), and 2 study drugs for Treatment Group 3 (ie, oral QD LEN and F/TAF), excluding long acting LEN used for oral lead-in.

Adherence (%) of QD study drug(s) will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{Total \text{ No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$= 100 \times \frac{\sum\sum \text{No. of pills taken at each dispensing period for each study drug}^{[1]}}{\sum\sum \text{No. of pills prescribed at each dispensing period for each study drug}^{[2]}}$$

[1] Number of pills taken at a distinct dispensing period for QD study drug(s) will be calculated as the minimum of (a) the daily number of pills prescribed multiplied by the duration of treatment of QD study drug(s) at the dispensing period of the same dispensing date, and (b) the number of pills taken (number of pills dispensed minus the number of pills returned). Total number of pills taken is determined by summing the number of pills taken from all evaluable dispensing periods for all QD study drug(s).

[2] Number of pills prescribed at a distinct dispensing period for QD study drug(s) will be calculated as the daily number of pills prescribed multiplied by the duration of treatment of QD study drug(s) at the dispensing period of the same dispensing date. Total number of pills prescribed is determined by summing the number of pills prescribed from all evaluable dispensing periods for all QD study drug(s).

The duration of treatment of QD study drug(s) at a dispensing period for the study drug is calculated as the minimum of (a) the last returned date of the study drug at a dispensing period, (b) date of premature discontinuation of the study drug, and (c) next pill dispensing date of the study drug, minus dispensing date of the study drug.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Adherence will be calculated for each subject for the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or using all available data for subjects ongoing on study drug by the data cut date.

Descriptive statistics for adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for subjects who return at least 1 bottle of randomized QD study drug, and who have calculable adherence in the Safety Analysis Set. No inferential statistics will be provided.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the All Safety Analysis Set. 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 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations (e.g., at least 1, with 1, 2, 3 or more important protocol deviations), and the total number of important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by treatment group for the Safety Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, 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 treatment group and overall 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.

Statistical comparison across treatment groups will be performed. For categorical data, the Cochran-Mantel-Haenszel (CMH) test will be used to compare across treatment groups except for gender identity and sexual orientation. For continuous data, the 2-sided Kruskal-Wallis test will be used to compare across treatment groups.

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

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables:

- HIV-1 RNA (log_{10} copies/mL)
- HIV-1 RNA categories (copies/mL): (a) ≤ 100,000, (b) > 100,000
- CD4 cell counts (/uL)
- CD4 cell counts categories (/uL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)

The summary of these baseline disease characteristics will be provided for the Safety Analysis Set. Statistical comparison across treatment groups will be conducted similarly as described for the demographic and baseline characteristics.

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

5.3. Medical History

General medical history data will be collected at screening including HIV-1 disease-related events. General medical history data will be coded and listed.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purposes.

6.1.1. US FDA-defined Snapshot Algorithm

The analysis window at Week 54 is defined as from Study Day 323 to Study Day 413, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- HIV-1 RNA < 50 copies/mL: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 54 analysis window
- HIV-1 RNA ≥ 50 copies/mL: this includes subjects
  - Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 54 analysis window, or
  - Who do not have on-treatment HIV-1 RNA data in the Week 54 analysis window and
    - Who discontinue study drug prior to or in the Week 54 analysis window due to lack of efficacy, or
    - Who discontinue study drug prior to or in the Week 54 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- No Virologic Data in the Week 54 analysis window: this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 54 analysis window because of the following:
  - Discontinuation of study drug prior to or in the Week 54 analysis window due to AE or death (regardless of whether the last available on-treatment HIV-1 RNA < 50 copies/mL or not) or,
  - Discontinuation of study drug prior to or in the Week 54 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,
  - Missing data during the window but on study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in Section 12 (Appendix 2).

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

The proportion of subjects with HIV-1 RNA < 50 copies/mL as determined by the US FDA-defined snapshot algorithm at Week 54 will be based on the FAS. Point estimates ($P_1 - P_2$) and its 95% confidence interval (CI) for the difference in the response rates between each of the LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportion as described as follows {Koch 1989}, stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL):

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} * SE(P_1 - P_2),$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference,

  where $d_h = p_{1h} - p_{2h}$ is the difference in the response rate between of the LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) in stratum h (h=1 to 4).

- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group

  for each stratum where n_{1h} and n_{2h} are the sample sizes of the LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) in stratum h.

- $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 \left[\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1} \right]}{(\sum w_h)^2}}$, where $p_{1h}^* = \frac{m_{1h} + 0.5}{n_{1h} + 1}$ and

  $p_{2h}^* = \frac{m_{2h} + 0.5}{n_{2h} + 1}$. m_{1h} and m_{2h} are the number of subjects with HIV-1 RNA < 50 copies/mL in the LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) in stratum h.

- $\alpha = 0.05$ for this study

- $Z_{(1-\alpha/2)} = Z_{0.9750} = 1.96$ is the 97.50th percentile of the normal distribution

Note that if the computed lower confidence bound is less than –1, the lower bound is defined as –1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 54 will be summarized. The associated p-values will be estimated based on the CMH test stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

6.1.3. Secondary Analysis for the Primary Efficacy Endpoint

A secondary analysis based on the Week 54 PP analysis set will also be performed to evaluate the robustness of the primary analysis of the primary endpoint. Subjects excluded from the Week 54 PP analysis set will be determined before database lock.

6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 28, 38, 54, and 80

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 28 as determined by the US FDA-defined snapshot algorithm has been performed in the Week 28 analyses and will not be repeated here. The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 38 as determined by the US FDA-defined snapshot algorithm will be analyzed using the same method as the primary analysis for the primary endpoint based on the FAS.

The proportion of subjects with HIV-1 RNA < 50 copies/mL as determined by the US FDA-defined snapshot algorithm at Week 80 will not be summarized for the Week 54 interim analysis as the majority of subjects will not have reached the timepoints of interest.

6.2.1. Analysis of the Secondary Efficacy Endpoints

The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell counts will be based on the FAS and summarized up to the visits with available data using descriptive statistics. The differences in changes from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count between each of the LEN-containing treatment groups (Treatment Groups 1-3) and the B/F/TAF group (Treatment Group 4) and the associated p-values and 95% CIs will be constructed using analysis of variance (ANOVA) models adjusting for the baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

Mean ± 95% CI and median (Q1, Q3) of the change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell counts will be plotted by visit.

6.3. Other Efficacy Endpoints

6.3.1. Proportion of Subjects with HIV-1 RNA < 50 copies/mL by Missing = Failure and Missing = Excluded Analyses

Number and percentage of subjects with HIV-1 RNA < 50 copies/mL by visit will be analyzed using the following 2 analyses:

- Missing = Failure (M = F):

  In this approach, missing data will be treated as virologic failure and summarized into the "missing" category (see list of HIV-RNA categories below). Results will be summarized by treatment group for all visits up to Week 54.

- Missing = Excluded (M = E):

  In this approach, missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of subjects in the FAS with nonmissing HIV-1 RNA value at that visit. Results will be summarized by treatment group for all visits up to Week 54.

For both M = F and M = E analyses, the number and percentage of subjects with HIV-1 RNA in the following categories will be summarized based on the FAS:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL
- Missing (only applicable to M = F analysis)

Statistical comparison between each of the LEN-containing treatment groups (Treatment Groups 1-3) and the B/F/TAF group (Treatment Group 4) will be performed. Point estimates and its 95% CIs will be estimated using stratum-adjusted MH proportion as described in Section 6.1.2. The associated p-values will be estimated based on the CMH test stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

6.4. Subgroup Analysis

Subgroups defined in Section 3.4.1 will be performed for the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US FDA-defined snapshot algorithm. Subgroup analysis will be performed on subjects who have reached Week 54 at the time for the Week 54 analysis in the FAS for on-treatment data. Results will be descriptive and the associated 95% CIs will be constructed using Exact method.

6.5. Changes from Protocol-Specified Efficacy Analyses

No change from protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

Safety data will be summarized for subjects in the Safety Analysis Set. All safety data collected up to the last exposure date for subjects who prematurely discontinued study drug or all available data for subjects who were still on study drug will be included in the table summary, unless specified otherwise. All collected data 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 Medical Dictionary for Regulatory Activities (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 are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. 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-subject 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 AEs met the definitions 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 Global Patient Safety (GLPS) 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 1 or both of the following:

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

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 dose 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 as follows:

- Subjects who receive SC injection: the AE onset date is the same as or after the month and year (or year) of the first dose date of study drug
- Subjects who do not receive SC injection:
  - The AE onset is the same as or after the month and year (or year) of the first dose date of study drug, and
  - The AE onset date is the same as or before the month and year (or year) of the last exposure date

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose 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 dose date of study drug will be considered treatment emergent.

When calculating the duration of event or time to onset, the following imputation rule will be used:

Missing start month/day: Jan 1/first day of the month will be used unless this is before the start date of study drug; in this case the study drug start date will be used;

Missing stop month/day: Dec 31/last day of the month will be used, unless this is after the last study date; in this case the last study date will be used.

Completely missing start or end dates will remain missing, with no imputation applied.

7.1.6. Summaries of Adverse Events and Deaths

TEAEs 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 subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All 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 treatment group, SOC and PT, and by PT only for the following AE categories:

- TEAEs
- TEAEs (by severity)
- TEAEs with Grade 3 or higher (by severity)
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher (by severity)
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to premature discontinuation of study
- TEAEs leading to death (by SOC and PT only)

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 summarizes by PT only, AEs will be summarized and listed by PT in descending order of total frequency.

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

- All AEs
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug
- All AEs leading to premature discontinuation of study

For each listing, whether the event is treatment emergent will be indicated.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Study Drug Related Injection Site Reactions

Additional analysis of AEs will be performed for injection site reaction (ISR) related to study drug, which is defined as an AE related to study drug reported as any event within the MedDRA HLT of "Injection Site Reactions". The following summaries will be provided for each SC injection visit (eg, Day 1, Week 28) and the overall for subjects in Treatment Groups 1 and 2.

- Number of subjects that received SC injection(s)
- Number and percentage of subjects with study drug related ISRs
- Number and percentage of subjects with study drug related ISRs by grade
- Number and percentage of subjects with study drug related ISRs by PT

The denominator for the percentage calculation for the by visit summary and the overall summary will be based on the total number of subjects who receive at least 1 SC injection at the visit of interest and the total number of subjects who receive at least 1 SC injection at any injection visit, respectively.

Duration of the ISR will also be calculated and summarized. Duration of a given ISR event is defined as the ISR stop date minus the ISR onset date plus 1 day. For ISRs with ongoing stop date, stop date will be imputed as last study date or data cut date, whichever is the earliest. Duration of ISR events in days will be summarized using descriptive statistics.

A by-subject listing for study drug-related ISRs and the corresponding duration will be provided.

7.1.7.2. Study Drug Related Injection Site Induration and Nodules

Percentage of ongoing and resolved study drug releated injection site induration will be summarized for each SC injection (eg, Day 15, Week 28, and Week 54) and the overall at both subject-level and event-level.

For the subject-level summary, if a subject had more than one injection site indurations, the subject will be counted in the "Ongoing" category unless all study drug releated injection site induration events have been resolved.

For the event-level summary, duration of the resolved events will be summarized using descriptive statistics.

Study drug related injection site nodules will be summarized in the same manner as defined for study drug releated injection site induration.

A by-subject listing for study drug related injection site induration and nodules and the corresponding duration will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during 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 and will include data collected up to the last exposure date for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. 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. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL))

Toxicity grading for calcium will be applied based on the corrected values.

Estimated Glomerular Filtration Rate

The following formulae will be used to calculate the estimated glomerular filtration rate using Cockcroft-Gault formula ($eGFR_{CG}$):

$eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms and SCr is serum creatinine.

Low-Density Lipoprotein

The following formulae will be used to calculate the low-density lipoprotein (LDL) using Friedewald formula when cholesterol, high-density lipoprotein(HDL), and triglyceride for a given blood drawn are available:

LDL (mg/dL) = total cholesterol (mg/dL)– HDL (mg/dL) – triglyceride (mg/dL)/5;

The fourth generation LDL is calculated from above Friedewald formula. The third generation LDL is a direct measurement from blood drawn. Both generations of LDL will be listed in the listing. Only fourth generation LDL calculated from the Friedewald formula will be used for analysis.

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. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, 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 treatment group for selected laboratory test 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.

Median (Q1, Q3) of the change from baseline values for these selected laboratory tests will be plotted by treatment group and visit.

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 Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, 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.

For triglycerides, LDL (4th generation), and cholesterol, the 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 baseline at any postbaseline visit, up to last exposure date for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above 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 subjects in the study with the given response at baseline and each scheduled postbaseline visit.

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values.

A by-subject listing of treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities, respectively, 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 for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs as follows:

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

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose date 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-subject listing of vital signs will be provided by subject 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

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The WHO preferred name and drug code will be attached to the clinical database.

7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications are defined as any ARV medications taken prior to, during, or after the study (if collected). All nonstudy drug ARV medications will be listed. No inferential statistics will be provided.

7.4.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications are defined as non-ARV medications taken while a subject took study drug. Use of concomitant medications from Study Day 1 up to the last exposure date will be summarized (number and percentage of subjects) by treatment group, WHO drug class and preferred name. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class. For drugs with the same frequency, sorting will be done alphabetically.

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 the last exposure date
- The month and year of stop of the medication is before the first dose date of study drug

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

Summaries of non-ARV concomitant medications will be based on the Safety Analysis Set. No formal statistical testing is planned. A by-subject listing for all non-ARV concomitant medications will be listed and sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

7.5.1. Investigator Electrocardiogram Assessment

The investigators' assessment of ECG results (normal; abnormal, not clinically significant; abnormal, clinically significant) are collected at screening only. A by-subject listing for ECG assessment results will be provided by subject ID number.

7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy and subjects using/misusing any substances (eg, illicit drug) during the study, respectively. Physical examination was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the Safety Analysis set. No formal statistical testing is planned.

7.8. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analyses is planned.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Blood samples will be collected to determine PK (and metabolites, if applicable) in plasma at the following timepoints:

For Treatment Groups 1 and 2:

Plasma PK sampling will occur relative to dosing of LEN at the following time points for all subjects:

- Days 1, 2, and 8:
  - — Predose (within 30 minutes of dosing)
  - — A single timed PK sample between 1 and 6 hours postdose
- [redacted]
- At Day 15 and at all visits with SC LEN injections: A single predose PK sample will be collected
- Starting at Week 4 visit, at all visits without SC LEN injections: A single anytime PK sample will be collected.

CCI [redacted]

For Treatment Group 3:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits

CCI [redacted]

For Treatment Group 4:

- Starting at Day 1 visit, a single anytime PK sample will be collected at all study visits.

Only plasma CCI samples collected through Week 54 last patient last visit (LPLV) date were analyzed and included in the Week 54 interim analysis.

8.2. PK Analyses Related to Intensive PK Sampling

8.2.1. 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.

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 0 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_{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.

8.2.2. PK Parameters

CCI

CCI [redacted]

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
TAF	AUC_{tau}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}
TAF Week 38	$AUC_{last,ss}$, $t_{1/2}$, λ_z, $C_{max,ss}$, $T_{max,ss}$, $C_{last,ss}$, $T_{last,ss}$, $AUC_{tau,ss}$, $C_{tau,ss}$
TFV	AUC_{tau}, AUC_{last}, $t_{1/2}$, λ_z, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}
BIC Week 38	$AUC_{last,ss}$, $t_{1/2}$, λ_z, $C_{max,ss}$, $T_{max,ss}$, $C_{last,ss}$, $T_{last,ss}$, $AUC_{tau,ss}$, $C_{tau,ss}$
TFV-DP	AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}

8.2.3. Statistical Analysis Methods

Plasma concentration for LEN, TAF, TFV, BIC, and TFV-DP will be listed for all subjects and summarized by nominal time point for subjects in the PK Analysis Set, CCI [redacted] by treatment group and analyte.

PK parameters estimated for TAF, BIC, and TFV will be listed for all subjects. CCI [redacted]

Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by treatment group and analyte. Moreover, the geometric mean, 95% 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 0 at predose and one-half of the lower 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 and visit:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics
- [redacted]

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

- 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.

PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

The molecular weight of TFV-DP (447.17 g/mol) and the density of 5000 million cells/mL will be used in the conversion of concentration from ng/million cells to µmol/L; where the value in ng/million cells * (5000/447.17) results in the value in µmol/L or µM.

$$\frac{ng}{million\ cells} \times \frac{1\ nmol}{447.17\ ng} \times \frac{1\ \mu\boldsymbol{mol}}{1000\ nmol} \times \frac{5000\ million\ cells}{1\ mL} \times \frac{1000\ mL}{\boldsymbol{L}} = \frac{\mu mol}{L} = \mu M$$

8.2.4. Sensitivity Analyses

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

8.2.5. Changes from Protocol-Specified Pharmacokinetic Analyses

No change from the protocol-specified PK analyses is planned.

9. REFERENCES

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

Phoenix WinNonlin® 7.0 Pharsigh Corporation, Princeton, NJ, USA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Schedule of Assessments

	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	30, 90, 180 Day Follow-Up[d]	Early Termination[e]
Written Informed Consent	X													
Obtain demographic information	X													
Medical History	X													
Complete Physical Examination	X	X				X	X[f]		X		X			X
Symptom-Directed Physical Examination			X		X		X[g]	X		X		X	X	
Vital Signs[h] (including weight)	X	X	X		X	X	X	X	X	X	X	X	X	X
12-lead ECG (supine)	X													
Height	X													
Hematology[i], Chemistry[j], Lipid panel[k], Urinalysis and Urine Chemistry[l], CD4+ Cell Count	X	X	X		X	X	X	X	X	X	X	X	X	X

	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	30, 90, 180 Day Follow-Up[d]	Early Termination[e]
Urine Storage Sample		X	X		X	X	X	X	X	X	X	X		X
Serum Pregnancy Test[m]	X													X
Serum FSH[n]	X													
Urine Pregnancy Test[m]		X	X		X	X	X	X	X	X	X	X	X	X
HBV, HCV Testing	X													
HIV-1 Genotyping/ Phenotyping	X													
Plasma HIV-1 RNA	X	X	X		X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample	X	X	X		X	X	X	X	X	X	X	X	X	X
PK Plasma Collection[o]		X	X		X	X	X	X	X	X	X	X		
CCI														
Oral GS-6207 Dispensation[s]		X	X		X		X	X	X	X	X	X		

	Screening[a]	Day 1[b]	Day 2	CCI	Day 8	Day 15	Every 6 weeks from Week 4 to Week 28 ±2 Days	Week 38 ±2 Days	Week 54 ±2 Days	Week 64 ±2 Days	Week 80 ±2 Days	Post Week 80 Visits[c] ±6 Days	30, 90, 180 Day Follow-Up[d]	Early Termination[e]
Subcutaneous GS-6207 Administration[t]						X	X		X		X	X		
F/TAF Dispensation[u]		X					X	X	X	X	X	X		
TAF Dispensation[v]							X	X	X	X	X	X		
Bictegravir Dispensation[w]							X	X	X	X	X	X		
B/F/TAF Dispensation[x]		X					X	X	X	X				
Study Drug Accountability		X	X		X	X	X	X	X	X	X	X		
QoL Administration[y]		X				X	X		X		X			
Injection Site Reaction Assessment Worksheet[z]						X	X		X		X			
Adverse Events/ Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X	X	X

a Screening evaluations must be completed within 30 days prior to Day 1
b Day 1 tests and procedures must be completed prior to administration of the dose of study drug. Participants must begin dosing on the same day as Day 1
c Assessments will be performed post Week 80 (Week 90, Week 106, Week 116, Week 132, Week 142) and will continue to alternate between every 10 weeks and every 16 weeks with the visit window ±6 days.
d Participants may be required to return to the clinic for a 30, 90 and 180-Day Follow-Up Visit after Early Termination visit.
e Within 72 hours of permanently discontinuing study. Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care and refer participant to an appropriate HIV treatment facility.
f Complete physical exam is only required at Week 28
g Symptom directed physical to be completed at Weeks 4, 10, 16, and 22, as necessary
h Vital signs – blood pressure, pulse, respiration rate, temperature, and weight
i Hematology: CBC with differential and platelet count

j Chemistries: Alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, and uric acid. eGFR according to the Cockcroft-Gault formula

k Fasting is not required for the lipid panel

l Urinalysis and Urine Chemistry: including color & clarity, specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase and microscopic (if microscopic elements are seen), urine protein, albumin, creatinine, phosphate, calcium, magnesium and uric acid

m Women will have a serum test performed at Screening. Urine pregnancy test will only be done for women of childbearing potential. In Treatment Groups 1 and 2, urine pregnancy tests should be confirmed to be negative prior to subcutaneous GS-6207 administration. If any pregnancy test is positive, study drug should be immediately interrupted, and participant should come to the site for serum pregnancy test.

n FSH test is required for women who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

o PK collection: For Treatment Groups 1 and 2, plasma PK sampling will occur relative to dosing of GS-6207 at Days 1, 2 and 8 predose (within 30 minutes of dosing) and a single timed PK sample between 1 and 6 hours postdose. CCI At Day 15 and all visits with SC GS-6207, a single predose PK sample will be collected. Starting at Week 4 and at all visits without SC GS-6207, a single anytime PK sample will be collected. PK sampling will continue at visits past Week 80.
For Treatment Groups 3 and 4 participants, starting at Day 1, a single anytime PK sample will be collected at all study visits.

[redacted]

s Treatment Group 1 and 2 oral GS-6207 lead in at Day 1, Day 2 and Day 8. Treatment Group 3 will receive oral GS-6207 lead in at Days 1 and 2 and will begin oral daily GS-6207 at Day 3.

t Treatment Group 1 and 2 Subcutaneous administration at Day 15 and every 26 weeks

u Treatment Group 1, 2, and 3 F/TAF once daily for 28 weeks starting at Day 1. Treatment Group 3 participants will continue F/TAF until study completion.

v Treatment Group 1 daily oral TAF to be initiated at Week 28

w Treatment Group 2 daily oral BIC to be initiated at Week 28

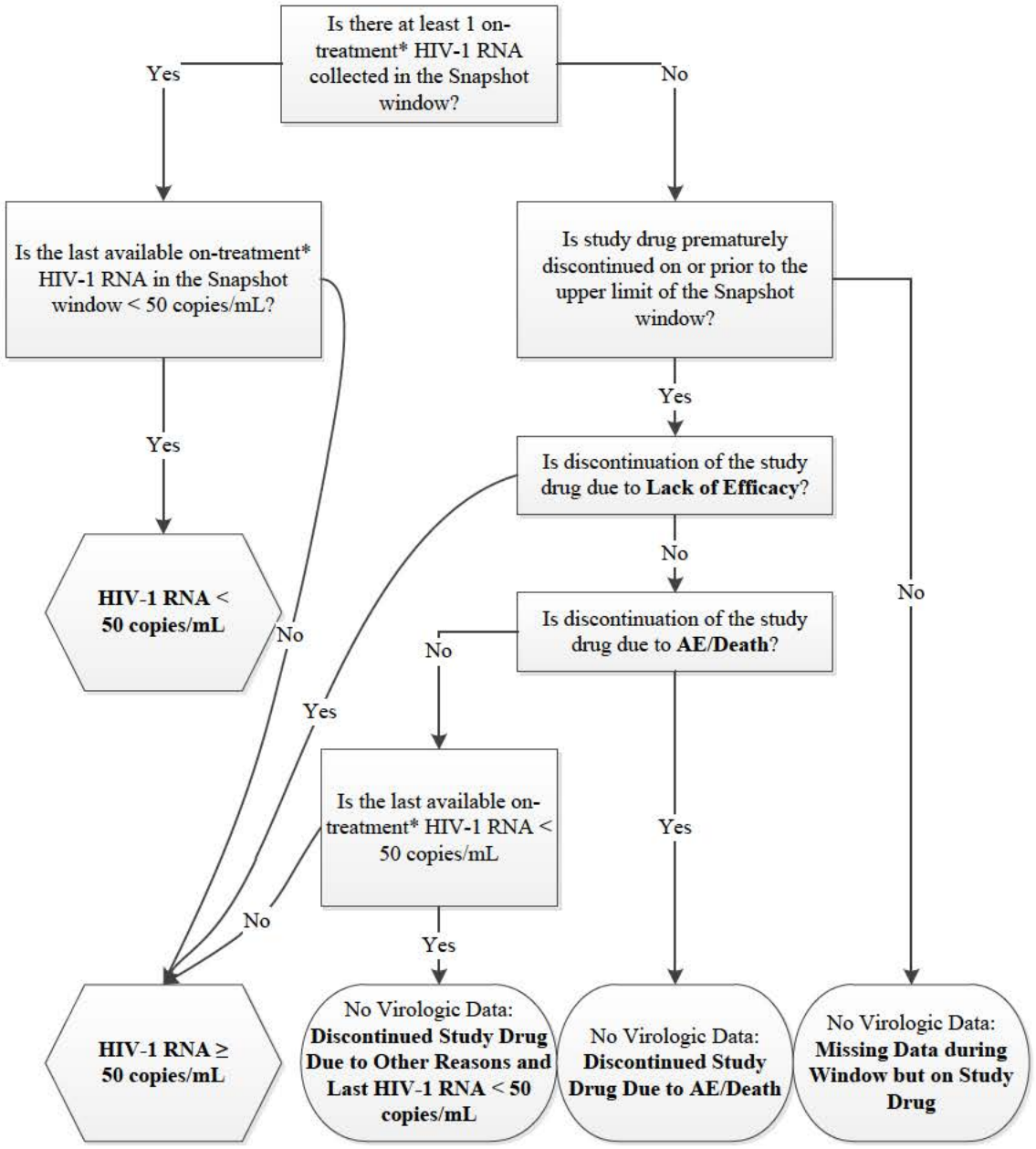
x Treatment Group 4 daily oral B/F/TAF

y Prior to completion of other study procedures, participants will complete HIVTSQ12, HIVDQoL, and EQ-ED-5L at Day 1 (except HIVTSQ12), Day 15 (HIVTSQ12 only), Week 4, Week 28, Week 54, Week 80. Injection Acceptability Scale and Numeric Pain Rating Scale to be completed at Day 15, Weeks 28, 54 and 80 (for Treatment Groups 1 and 2 participants only) after SC GS-6207 administration and completion of other study procedures.

z Provide Injection Site Reaction Assessment Worksheet and instruct the participants to measure and report injection site reactions following the administration of the subcutaneous injections (for Treatment Group 1 and 2 participants only)

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm(for Naïve Trial)

The following flowchart for US FDA-defined snapshot algorithm is based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment {U. S. Department of Health and Human Services 2015}



* On-treatment data include all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug.

Appendix 3. Programming Specification

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

   Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

   a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   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,

   AGE = the integer of the result in (c),

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened subjects refer to all subjects who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same subject is counted only once.

3) Screen failure subjects are the subjects who were 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) Subjects in the randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if the subject was never dosed.

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

7) Body mass index (BMI)

   BMI will be calculated only at baseline as follows:

   — BMI = (weight [kg]) / (height [meters]^2)

   Baseline height and weight will be used for this calculation if available.

8) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

   CMH test for nominal variable (Y), the p-value from the general association test should be used for nominal variables:

```
proc freq;
tables trt * Y /cmh; /*general association test*/
run;
```

   CMH test for ordinal variable (Y), the p-value from the row mean score test should be used for ordinal variables:

```
proc freq;
tables trt * Y / cmh2 ; /*row mean score test*/
run;
```

   Kruskal-Wallis test for continuous variable (Y):

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

9) For race and ethnicity, “Not Permitted”, “Missing”, or “Other” will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Kruskal-Wallis test).

10) Study Day 1, Last Dose Date and Last Exposure Date

    a) All the key dates were defined in Section 3.8.1.

11) Study Day 1 and Last Dose Date

    a) All the key dates were defined in Section 3.8.1.

    b) Study Day 1 is defined as the earliest of the dose start dates from any Study Drug Administration eCRF (ie, EX, EX_ARV or EX_IV).

    c) Last Dose Date is defined for subjects who prematurely discontinued study drug according to Study Drug Completion eCRF(ie, SDRGCOMP).

        i) For subjects who receive SC injection(ie, A subject has data in EX_IV.), the last dose date is defined as the latest nonmissing end date of the study drug used with LEN (ie, the last dose date in EX_ARV).

        ii) For subjects who do not receive SC injection(ie, A subject has no data in EX_IV.), the last dose date is defined as the earliest of the last dose date of any study drug (ie, the earliest of last dose date in EX or EX_ARV).

d) Study drug administration: Oral reload will be recorded as an "Unscheduled" visit in the Study Drug Administration eCRF. Subjects with oral reload prior to the 1st dose of SC have "Unscheduled" dosing visits occurred prior to Day 15 visit. Subjects who received a total of 5 tablets of LEN (300 mg) (ie, 2 x 300 mg LEN tablets each for the first 2 days and 1 x 300 mg LEN tablet on the 8th day) prior to "Unscheduled" dosing visits followed by Day 15 visit will be classified as oral reload due to missing scheduled SC dosing. Otherwise, subjects will be classified as oral reload due to missing scheduled oral dosing visit.

12) Adherence to QD Study Drug(s)

a) Adherence based on 1 study drug(Treatment Groups 1, 2, and 4):

$$\text{Adherence (\%)} = 100 \times \frac{Total \text{ No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$= 100 \times \frac{\sum \text{No. of pills taken at each dispensing period for each study drug}^{[1]}}{\sum \text{No. of pills prescribed at each dispensing period for each study drug}^{[2]}}$$

b) Adherence based on 2 study drugs(Treatment Group 3):

$$\text{Adherence(\%)} = 100 \times \frac{\text{Total No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$= 100 \times \frac{\sum\sum \text{No. of pills taken at each dispensing period for each drug}^{[1]}}{\sum\sum \text{No. of pills prescribed at each dispensing period for each drug}^{[2]}}$$

13) Efficacy Analysis

a) For categorical efficacy response (eg, Subjects with HIV-1 RNA < 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) and its 95% CIs are calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) (see SAP Section 6.2 and 6.3 for details). The following SAS code will be used to compute p-value, where *brnac* is the baseline HIV-1 RNA stratum, *trtgrp* is the treatment, and *response* is the categorical efficacy response.

```
proc freq data=adeff;
   tables brnac*trtgrp*response/cmh; /*p value from general
   association*/
run;
```

b) All the ANOVA model for continuous efficacy variable (eg, CD4+): The differences in changes from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count between treatment groups and the associated 95% CI will be constructed using an ANOVA, including baseline HIV-1 RNA stratum *brnac*, region stratum *region*, and treatment *trtgrp* as fixed effects in the model.

```
proc glm data=adeff;
   class brnac region trtgrp;
   model CD4=brnac region trtgrp;
   lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

14) Listing for US FDA-defined snapshot outcome:

In addition flag the values of HIV-1 RNA < 50 or ≥ 50 copies/mL for virologic outcomes.

Flag the last available HIV-1 RNA value while on treatment for the following categories:

a) HIV-1 RNA ≥ 50 copies/mL - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL

b) No virologic Data - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL

15) Injection site reaction (ISR)

a) To summarize ISRs by injection visit, each study drug related ISR will be associated with one injection visit (eg, Day 15 SC injection, Week 28 SC Injection, Week 54 SC injection) based on the start date of the ISR. If the start date of the ISR is on or after a given injection visit date and prior to the next injection visit date, if available, the ISR will be associated with that injection visit.

b) For ISR summarized by PT:

i) For the overall summary (ie, subjects received at least one injection), multiple ISRs with the same PT will only be counted once per subject for each PT.

ii) For by visit summary (ie, subjects received injection for a given injection visit), multiple ISRs associated with the injection visit of interest with the same PT will only be counted once per subject for each PT.

c) For ISR summarized by grade:

i) For the overall summary (ie, subjects received at least one injection), the most severe grade based on all ISRs will be used.

ii) For by visit summary (subjects received injection for a given injection visit), the most severe grade from all ISRs associated with the injection visit of interest will be used.

16) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken on or after first dose date) will be flagged in "Antiviral Medication" listings.

17) Graded Laboratory Abnormalities Summary

18) 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 (Hb)	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)
	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)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
Urinalysis	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative)

19) Clarification for "Pharmacokinetic Sampling Details and Concentrations" listings

- "Sample age" will be added in this listing, defined as the duration in days between sample collection date and assay date, ie, sample age = assay date – sample collection date + 1.

- Scheduled PK sampling time for intensive PK samples at predose is 5 mins prior to dosing time.

- SAMTIME is calculated as the duration in hours between the dosing time before sample collected and sample collection time, except for intensive PK samples at predose. SAMTIME for intensive PK samples at predose is calculated as the duration in hours between the dose time on the same day (ie, right after the predose sample collection) and sample collection time.

GS-US-200-4334-Week54-SAP-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	26-Oct-2021 19:20:03
PPD	Clinical Pharmacology eSigned	27-Oct-2021 02:47:41
PPD	Clinical Research eSigned	27-Oct-2021 05:36:46