GILEAD

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Randomized, Double-Blinded, Placebo Controlled, Multi-Cohort Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-6207 administered subcutaneously in HIV-1 Infected Subjects
Name of Test Drug:	Lenacapavir (LEN; GS-6207)
Study Number:	GS-US-200-4072
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ART	antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CAI	capsid inhibitor
CBC	complete blood count
CCG	CRF Completion Guidelines
CI	confidence interval
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GLPS	Global Patient Safety - previously Pharmacovigilance & Epidemiology (PVE)
GLSM	geometric least-squares means
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
ID	identification
INSTI	integrase strand transfer inhibitor
LEN	lenacapavir; previously referred to as GS-6207
LOQ	limit of quantitation

LTT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
NLP	Natural Language Processing
NNRTI	non-nucleoside reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear concentration
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PT	preferred term
Q1, Q3	first quartile, third quartile
RNA	ribonucleic acid
RT	reverse transcriptase
SAE	serious adverse event
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
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{0-t}	area under the concentration versus time curve from time zero to time t
AUC_{inf}	area under the concentration versus time curve from time zero to infinity
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_t	observed drug concentration at time t
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
CL/F	apparent oral clearance after administration of the drug: at steady state: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
V_z/F	apparent volume of distribution 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}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1.   INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-200-4072. This SAP is based on the study protocol amendment 4 dated 13 June 2019 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR. Throughout the text of this SAP, the study treatment for Part A is referred to as lenacapavir (LEN; previously referred to as GS-6207); the designation GS-6207 is used in preprogrammed tables, figures, and listings (ie, for treatment groups and PK analytes.)

1.1.   Study Objectives

Part A (LEN Cohorts 1-5)

The primary objective of this study is as follows:

- To evaluate the short-term antiviral activity of LEN compared to placebo LEN, with respect to the maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment (ART) naïve or are experienced but capsid inhibitor (CAI) naïve

The secondary objectives of this study are as follows:

- To investigate the safety and tolerability of LEN as compared to placebo LEN in HIV-1 infected subjects

- To characterize the plasma pharmacokinetics (PK) of LEN in HIV-1 infected subjects

- To characterize the PK/pharmacodynamics (PK/PD) relationship between LEN concentration and the viral dynamics of HIV-1

- To determine the number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 at each dose level

- To examine any emergence of CAI resistance

Part B (TAF Cohorts 6-8)

The primary objective of this study is as follows:

- To evaluate the short-term antiviral activity of tenofovir alafenamide (TAF) with respect to the maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are ART naïve or are experienced but without resistance to TAF.

The secondary objectives of this study are as follows:

- To investigate the safety and tolerability of TAF in HIV-1 infected subjects

- To characterize the PK of TAF and its metabolites in HIV-1 infected subjects

- To examine any emergence of TAF resistance

CCI

1.2.   Study Design

This is a Phase 1b study with 2 parts. Part A (LEN Cohorts 1-5) is a randomized, double-blind, and placebo-controlled study of LEN. Part B (TAF Cohorts 6-8) is a single-arm study of TAF. Up to approximately 64 subjects (Part A: up to 5 cohorts of 8 subjects; Part B: up to 3 cohorts of 8 subjects) will be randomized/enrolled.

Treatment Groups and Dosing

Part A:

Subjects will be randomized centrally within a cohort in a 3:1 ratio to receive active LEN (n 6) or placebo (n 2). A single dose of LEN or placebo will be administered as a subcutaneous (SC) injectable free acid suspension in the morning without regard to food. LEN doses may be administered as multiple SC injections at different abdominal sites. The doses to be evaluated in Cohorts 2 through 5 will be determined based on cumulative safety (through at least Day 14), available PK, and viral kinetic data from previous cohorts, as well as available safety (through at least Day 14) and PK data from Study GS-US-200-4070 (Phase 1, first-in-human, single ascending dose study of GS-6207 SC suspension formulation, in which GS-6207 30 to 450 mg was administered subcutaneously). As such, Cohorts 2-5 may be initiated in parallel. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses either in this study or in Study GS-US-200-4070. The Sponsor may elect to hold dosing or stop study enrollment at any time based on review of preliminary safety and PK data. The protocol prespecified doses and the corresponding number of injections for each cohort are provided below.

Cohort	Protocol Prespecified Dose of LEN or Placebo	Number of Injections
1	150 mg	1
2	50 mg	1
3	450 mg	3
4	20 mg	1
5	750 mg	5

Part B:

A single dose of TAF will be administered orally in the morning under fasted conditions on Day 1. The doses to be evaluated in Cohorts 7-8 will be determined based on cumulative safety (through at least Day 14), available PK, and viral kinetic data from previous cohorts. Selected doses will be either lower than, or no more than 3-fold higher than, previously evaluated doses in this study. Cohorts 7 and 8 may be run in parallel.

The protocol prespecified dose and actual dose used for each cohort are provided below. Cohort 8 was not initiated due to observed antiretroviral activity from Cohorts 6 and 7 which did not demonstrate durable activity over 10 days.

Cohort	Protocol Prespecified Dose of TAF	Actual Dose of TAF
6	200 mg	200 mg[1]
7	Up to 600 mg	600 mg[1]
8	Up to 600 mg	Did not enroll

1   Subjects enrolled in Cohort 6 (200 mg) and Cohort 7 (600 mg) will be given 8 and 24 tablets of TAF 25 mg tablet, respectively.

All subjects in Part A and Part B will initiate once-daily bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF, 50/200/25 mg) on Day 10 and be treated to Day 225.

Key Eligibility Criteria

Subjects with chronic HIV-1 infection who meet the following criteria:

- Plasma HIV-1 RNA ≥ 5,000 copies/mL but ≤ 400,000 copies/mL and CD4 cell count > 200 cells/mm^3

- Treatment naïve or experienced but integrase strand transfer inhibitor (INSTI) naïve and CAI naive (Part A only), and have not received any ART within 12 weeks of screening

- Screening genotype report must show sensitivity to B/F/TAF to allow TAF monotherapy (Part B) and initiation of B/F/TAF on Day 10 (Part A and Part B)

- Screening genotype report must show sensitivity to at least one agent in either non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) class to allow its use as part of standard of care oral ART in the future

- Have adequate renal function (estimated glomerular filtration rate [eGFR] ≥ 70 mL/min)

- No clinically significant abnormalities in electrocardiogram (ECG) at Screening

- Not pregnant or lactating

- Willing to initiate B/F/TAF on Day 10 after completion of all assessments

Schedule of Assessments

In Part A, following screening and Day 1 visits, subjects will be required to visit the clinic on Days 2, 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197, and 225.

In Part B, following screening and Day 1 visits, subjects will be required to visit the clinic on Days 2, 3, 4, 5 (if possible), 6 (if possible), 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197, and 225.

For both Part A and Part B, adverse events (AEs), concomitant medications, complete or symptom-directed physical examinations, and HIV-1 RNA will be performed at Screening, Day 1, and all subsequent study visits. CD4 cell count will be performed at Screening, Day 1, Day 10, Day 29, and all subsequent study visits. Other laboratory analyses (hematology, chemistry, and urine chemistry) will be performed at Screening, Days 1, 3, 7, 10, 14, and all subsequent study visits. Fasting is required for laboratory analyses at Days 1, 3, 7, 10, 85, 169, and 225. ECGs will be performed at Screening, Days 1 (predose), 2, 10, 29, 57, 85, 169, and 225.

Additionally, in Part A, blood samples will be collected for genotypic and phenotypic testing of HIV-1 capsid and for determining PK of LEN. In Part B, blood samples will be collected for genotypic and phenotypic testing of HIV-1 reverse transcriptase (RT) and for determining PK of TAF and tenofovir (TFV). In Part B, the peripheral blood mononuclear concentration (PBMC) PK samples will be collected to determine PK of tenofovir diphosphate (TFV-DP).

Details regarding study procedures could be found in Appendix 1.

1.3.   Sample Size and Power

Part A

A sample size of 6 subjects in each LEN treatment group and a total of 10 placebo subjects from all cohorts combined will provide 99% power to detect a treatment difference of 2.79 $\log_{10}$ copies/mL in maximum reduction of HIV-1 RNA between at least one of the LEN treatment groups and the placebo group. In this power analysis, it is assumed that a common standard deviation (SD) for maximum reduction in HIV-1 RNA is 0.526 $\log_{10}$ copies/mL (based on Study GS-US-141-1219) and a 2-sided t-test is conducted at an alpha level of 0.05.

Part B

A sample size of 8 subjects in each TAF treatment group and a total of 10 subjects in the placebo group will provide 99% power to detect a treatment difference of 1.43 $\log_{10}$ copies/mL in maximum reduction of HIV-1 RNA between at least one of the TAF treatment groups and the placebo group from Part A of the study. In this power analysis, it is assumed that a common SD for maximum reduction in HIV-1 RNA is 0.52 $\log_{10}$ copies/mL (based on Studies GS-US-120-0104 and GS-US-120-1101) and a 2-sided t-test is conducted at an alpha level of 0.05.

2.   TYPE OF PLANNED ANALYSIS

2.1.   Interim Analyses

For the purpose of dose selection(s), planned interim analyses were conducted by the Sponsor based on the analysis schedule defined in Section 8.9 of the protocol. A few individuals from the Sponsor were unblinded to assess the interim safety, efficacy, and PK (if available) of study drug. Details are defined in a charter.

2.2.   Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

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, SD or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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

Data from Part A (LEN cohorts) and Part B (TAF cohorts) will be summarized and listed separately.

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

3.1.   Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The assignment of subjects to analysis sets will be done before the study blind is broken for analysis. 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 Enrolled Analysis Sets

All Enrolled Analysis Set includes all subjects who either (a) are randomized into Part A of the study after screening or (b) receive a study subject identification number in Part B of the study after screening.

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

3.1.2.   Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who are randomized/enrolled and receive at least 1 full dose of study drug. This is the primary analysis set for efficacy analyses. Subjects with major eligibility violations that are identifiable based on pre-randomization/enrollment characteristics may be excluded.

3.1.3.   Safety Analysis Set

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

3.1.4.   Pharmacokinetic Analysis Set

The PK Analysis Set will be defined separately for each analyte of interest (ie, LEN, TAF, and its metabolite TFV). Each PK Analysis Set will include all subjects who are randomized/enrolled, receive at least 1 dose of study drug, and have at least 1 nonmissing postdose concentration value reported by the PK laboratory for the respective analyte. This is the primary analysis set for all PK analyses.

3.1.5.   Peripheral Blood Mononuclear Cell Pharmacokinetic Analysis Set

The PBMC PK Analysis Set will include all subjects who are enrolled in Part B of the study, receive at least 1 dose of study drug, and have at least 1 nonmissing TFV-DP concentration. The PBMC PK Analysis Set will be used for PK analyses of TFV-DP.

3.2.   Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were randomized/enrolled. For all other analyses, subjects will be grouped according to the actual treatment received. Data from the placebo recipients in Part A of the study will be combined to form one placebo group for the purpose of analysis.

Subjects will be grouped by treatment dose and pooled treatments (all LEN for Part A and all TAF for Part B).

For Part A enrollment, disposition, protocol deviations, demographics, baseline disease characteristics, and HIV-1 RNA < 50 copies/mL by visit tables, an additional total column for all Part A subjects will be included.

For efficacy tables and PK tables, pooled treatment groups will not be included.

3.3.   Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects.
No covariates will be included in the analyses.

3.4.   Examination of Subject Subgroups

There are no prespecified subject subgroupings for analyses.

3.5.   Multiple Comparisons

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

3.6.   Missing Data and Outliers

3.6.1.   Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2 and for prior (disease-specific 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. Therefore, the following conventions will be used for the imputation of full date of birth:

- If year of birth is collected, "01 July" will be imputed as the day and month of birth

- If year of birth is missing, 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, age derived based on date of birth and the Day 1 visit date will be used instead. If a randomized/enrolled subject was not dosed with any study drug, the randomization/enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance) 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 LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 20 and < 2.0, values of 19 and 19.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

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

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

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

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

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

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

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

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

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

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

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

3.8.   Analysis Visit Windows

3.8.1.   Definition of Study Day, Baseline, and Postbaseline

Study day will be calculated from the first dose date of study drug and derived as follows:

- For postdose study days: Assessment Date   First Dosing Date + 1

- For days prior to the first dose: Assessment Date   First Dosing Date

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

Baseline is defined as the last available off-treatment value collected on or prior to the first dose of study drug (ie, start time of injection).

Postbaseline is defined as any value collected after the first dose of study drug (ie, start time of injection).

Last Study Date is the latest clinic visit dates and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF.

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 and vital signs are provided in Table 3-1.

Table 3-1. **Analysis Windows for HIV-1 RNA[a] and Vital Signs**

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline		(none)	≤ Dose time on Day 1 [1][b]
Day 2	2	> Dose time on Day 1 [2][b]	2
Day 3	3	3	3
Day 4	4	4	5
Day 7	7	6	7
Day 8	8	8	8
Day 9	9	9	9
Day 10	10	10	11
Day 14	14	12	21
Day 29	29	22	35
Day 43	43	36	49
Day 57	57	50	70
Day 85	85	71	98
Day 113	113	99	126
Day 141	141	127	154
Day 169	169	155	182
Day 197	197	183	210
Day 225	225	211	(none)

a   The analysis window for HIV 1 RNA only applies to the change from baseline in HIV 1 RNA analysis. When defining the maximum reduction from baseline in HIV 1 RNA and percentage of subjects ever achieving HIV 1 RNA < 50 copies/mL by Day 10, all HIV 1 RNA data will be used ignoring the analysis window.
b   For vital signs as no times (only dates) were collected, Day 1 vital signs considered completed prior to administration of the dose of study drug.

The analysis windows for CD4+ cell count and CD4% are provided in Table 3-2.

Table 3-2.   **Analysis Windows for CD4+ and CD4%**

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline		(none)	$\leq$ Dose time on Day 1
Day 10	10	> Dose time on Day 1	19
Day 29	29	20	35
Day 43	43	36	49
Day 57	57	50	70
Day 85	85	71	98
Day 113	113	99	126
Day 141	141	127	154
Day 169	169	155	182
Day 197	197	183	210
Day 225	225	211	(none)

The analysis windows for hematology, chemistry (including estimated glomerular filtration rate using Cockcroft-Gault formula [eGFR$_{CG}$]), and urinalysis are provided in Table 3-3.

Table 3-3.   **Analysis Windows for Hematology, Chemistry, Urinalysis, and eGFR$_{CG}$**

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline		(none)	$\leq$ Dose time on Day 1
Day 3	3	> Dose time on Day 1	4
Day 7	7	5	8
Day 10	10	9	11
Day 14	14	12	21
Day 29	29	22	35
Day 43	43	36	49
Day 57	57	50	70
Day 85	85	71	98
Day 113	113	99	126
Day 141	141	127	154
Day 169	169	155	182
Day 197	197	183	210
Day 225	225	211	(none)

The analysis windows for 12-lead ECG are provided in Table 3-4.

Table 3-4.   **Analysis Windows for ECG**

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline		(none)	≤ Dose time on Day 1
Day 2	2	> Dose time on Day 1	5
Day 10	10	6	19
Day 29	29	20	42
Day 57	57	43	70
Day 85	85	71	126
Day 169	169	127	196
Day 225	225	197	(none)

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

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

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

- For baseline, the last nonmissing value on or prior to the first dose of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data (except for HIV-1 RNA, see below), or the measurement with the lowest severity (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 count and CD4% in which the latest record will be selected and HIV-1 RNA level [see below]).

    If there are 2 records that are equidistant from the nominal day, the later record will be selected.

    If there is more than 1 record on the selected day, the average will be taken for continuous data (except for HIV-1 RNA, see below) and the worst severity will be taken for categorical data, unless otherwise specified.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both "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

A summary of subject enrollment will be provided by country, investigator, treatment group, and overall within Part A (all LEN and all subjects) and Part B (all TAF). The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

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

A summary of subject disposition will present the number of subjects screened and the number of subjects who met all eligibility criteria but were not enrolled with reasons subjects not enrolled. Additional summaries of subject disposition will be provided by treatment group and overall within Part A (all LEN and all subjects) and Part B (all TAF) as well as the number and percentage of subjects in each of the categories listed below:

- All Enrolled Analysis Set

- Safety Analysis Set

- Full Analysis Set

- Completed study drug

- Did not complete study drug with reasons for premature discontinuation of study drug

- Completed study

- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of 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 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 (including those related to coronavirus disease 2019 [COVID-19])

- Reasons for screen failure (will be provided by screening ID number in ascending order)

- Analysis set status (indicating whether or not a subject is included in a given analysis set)

4.2.   Extent of Study Duration

A subject's extent of exposure to LEN or TAF will be generated from the Study Drug Administration eCRF. Exposure data of LEN and TAF will be listed.

Due to the long-acting feature of the study drug, a summary of the extent of study duration (defined as last study day minus first dose date of study drug plus 1) will be provided, summarizing the number of subjects still in study up to each nominal visit. The total study duration will also be summarized using descriptive statistics.

B/F/TAF is provided by Sponsor with dispensing information recorded on the Accountability eCRF. Accountability data of B/F/TAF will be listed.

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 based on the 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.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, violation of select inclusion/exclusion criteria) will be summarized by treatment group and overall for the All Enrolled Analysis Set. By-subject listings will be provided for those subjects with important protocol deviations and for those with either important protocol deviations or non-important protocol deviations related to COVID-19.

4.4.   Missing Protocol-Specified Information due to COVID-19

A by-subject listing of subjects affected by the COVID-19 pandemic will be provided by subject ID number and comment visit in ascending order along with determination of if the subject missed the visit due to COVID-19 or had a virtual visit due to COVID-19.

The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 2.

5.   BASELINE CHARACTERISTICS

5.1.   Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/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.

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

5.2.   Other Baseline Characteristics

Other baseline characteristics include HIV-1 RNA (log$_{10}$ copies/mL), CD4 cell count (/μL), CD4 percentage (%), mode of infection (HIV risk factors), HIV disease status, ever participated in pre-exposure prophylaxis (Yes/No), ever participated in post-exposure prophylaxis (Yes/No), and ART status (experienced/naïve). These baseline 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. The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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 and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). Data on general medical history will be listed.

6.   EFFICACY ANALYSES

6.1.   Primary Efficacy Endpoint

The primary efficacy endpoint is the maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) from Day 1 through Day 10.

Data from the placebo recipients in Cohorts 1-5 will be combined to form one placebo group. Each of the LEN treatment groups will be compared to the pooled placebo group with respect to the primary efficacy endpoint using the 2-sided t-test conducted at an alpha level of 0.05. Pairwise comparison of the maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) from Day 1 though Day 10 among all LEN treatment groups will also be performed. The analysis will be conducted using the FAS.

6.2.   Secondary Efficacy Endpoint

6.2.1.   Number and Percentage of Subjects Ever Achieving HIV-1 RNA < 50 copies/mL by Day 10 (Part A)

The number and percentage of subjects ever achieving HIV-1 RNA < 50 copies/mL by Day 10 will be summarized by treatment group for Part A using the FAS. Fisher exact test will be used for comparison between treatment groups.

6.3.   Other Efficacy Endpoints

6.3.1.   Definition of Other Efficacy Endpoints

Other efficacy endpoints include:

- Change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL) by Day 10

- Number and percentage of subjects with HIV-1 RNA < 50 copies/mL

- Change from baseline in CD4 cell count (/μL)

6.3.2.   Analysis of Other Efficacy Endpoints

Baseline values, values at each visit, and the change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL) by visit will be summarized by treatment group. Pairwise comparison of the change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL) among all treatment groups and placebo at each visit through Day 10 will be performed in the same manner as that of the primary efficacy endpoint.

Mean ± 95% confidence interval (CI) and median (Q1, Q3) of the change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL) will be plotted to Day 10 using a line plot by treatment group and visit.

Number and percentage of subjects with HIV-1 RNA < 50 copies/mL by visit will be analyzed using the missing   excluded method, where missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both numerator and denominator in the computation). The denominator for percentages at a visit is the number of subjects in the FAS with nonmissing HIV-1 RNA value at that visit. No statistical testing is planned. The number and percentage of subjects with HIV-1 RNA in the following categories will be summarized:

- < 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

Baseline values, values at each visit, and the change from baseline in CD4 cell count (/μL) by visit will be summarized by treatment group. No statistical testing is planned.

All efficacy endpoints will be conducted using the FAS.

6.4.   Changes from Protocol-Specified Efficacy Analyses

Due to differences in the treatment regimens in Part A (subcutaneous injection) and Part B (oral administration), the TAF (Part B) oral dose groups will not be compared to the placebo injection group in Part A with respect to the efficacy endpoints.

7.   SAFETY ANALYSES

7.1.   Adverse Events and Deaths

7.1.1.   Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and 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, or 4 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 any AE with an onset date on or after the study drug start date.

7.1.5.2.   Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first 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 if the AE onset is the same as or after the month and year (or year) of the first dose date of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of study drug, will be considered to be treatment emergent (and included in both TEAE summaries up to Day 10 and throughout the study.) 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 (and included in both TEAE summaries up to Day 10 and throughout the study).

7.1.6. Summaries of Adverse Events and Deaths

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

7.1.6.1.   Summaries of AE Incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group for TEAEs with onset date reported up to Day 10 (prior to the B/F/TAF first dose date) and throughout the study, respectively. 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 SOC, HLT (if applicable), PT, and treatment group.

- TEAEs

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs with Grade 3 or higher (by severity)

- TE treatment-related AEs

- TE treatment-related AEs with Grade 3 or higher (by severity)

- TEAEs leading to death (ie, outcome of death)

- TE SAEs

- TE treatment-related SAEs

- TEAEs leading to premature discontinuation of study drug

- TEAEs leading to premature discontinuation of study

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 HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, for the AE categories described below, summaries will be provided by PT only in descending order of total frequency:

- TEAEs

- TE SAEs

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

- All AEs

- All SAEs

- All Deaths

- All AEs leading to death (ie, outcome of death)

- 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

- All AEs for COVID-19 and Suspected COVID-19 infection, defined as AE preferred terms of "Suspected COVID-19", "COVID-19", "COVID-19 pneumonia", or "Asymptomatic COVID-19"

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

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 throughout the study. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-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 Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values

- Values at each postbaseline visit

- Change from baseline at each postbaseline visit

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

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

7.2.2. Graded Laboratory Values

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

7.2.2.1.   Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline visit. 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 (note: in addition to summarizing abnormalities throughout the study, a separate table will summarize abnormalities reported up to Day 10, collected on or prior to the B/F/TAF first dose date)

- 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 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 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 and Disease-Specific Medications

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

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

7.4.1.   Prior and Disease-Specific Prior Medications

Prior and disease-specific prior medications are defined as any medications taken before a subject took the first study drug.

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

7.4.2.   Concomitant Medications

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

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

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

7.5.   Electrocardiogram Results

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

7.5.1.   Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

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

7.6.   **Other Safety Measures**

No additional safety measures are specified in the protocol.

7.7.   **Changes from Protocol-Specified Safety Analyses**

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

8.   PHARMACOKINETIC (PK) ANALYSES

8.1.   PK Sample Collection

Part A (Cohorts 1-5 LEN PK sampling)

Blood samples will be collected to determine LEN PK (and metabolites, if applicable) in plasma at the following time points relative to study drug dosing:

- Day 1: 0 (predose), 1, 2, 4, 8, 12, and 24 hours postdose

- Days 3, 4, 7, 8, 9, 10, 14, 29, 43, 57, 85, 113, 141, 169, 197, and 225 for a single anytime PK sample

Part B (Cohorts 6-8 TAF PK sampling)

Plasma PK samples will be collected to determine PK of TAF and its metabolite, TFV, at the following time points relative to study drug dosing:

- Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours postdose

- Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10 at approximately the same time in the morning as predose on Day 1

PBMC PK samples will be collected to determine PK of TFV-DP at the following time points relative to study drug dosing:

- Day 1: 0 (predose), 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose

- Days 4, 5 (if possible), 6 (if possible), 7, 8, 9, and 10 at approximately the same time in the morning as predose on Day 1

8.2.   PK Analyses Related to 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 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

PK parameters will be generated for all subjects for whom parameters can be derived. The analytes presented in Table 8-1 will be derived if data are available.

Table 8-1.   Study Treatments and Associated Analytes

Cohort	Treatment	Analyte
1	LEN 150 mg SC	LEN
2	LEN 50 mg SC	LEN
3	LEN 450 mg SC	LEN
4	LEN 20 mg SC	LEN
5	LEN 750 mg SC	LEN
6	TAF 200 mg tablet	TAF, TFV, TFV-DP
7	TAF 600 mg tablet	TAF, TFV, TFV-DP
8	Not conducted	

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2.   PK Parameters for Each Analyte

Analyte	Parameters
LEN	AUC_{0-t}, AUC_{inf}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, C_{D10}, T_{last}
TAF	AUC_{0-t}, AUC_{inf}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}
TFV	AUC_{0-t}, AUC_{inf}, AUC_{last}, $t_{1/2}$, λ_z, C_{max}, T_{max}, C_{last}, T_{last}
TFV-DP	AUC_{0-t}, AUC_{inf}, AUC_{last}, $t_{1/2}$, λ_z, C_{max}, T_{max}, C_{last}, T_{last}

8.3.   Statistical Analysis Methods

8.3.1.   General Considerations

All PK analyses will be summarized based on the PK Analysis Set for the analyte of interest with the exception of the summary of TFV-DP which will be based on the PBMC PK Analysis set.

Individual subject concentration data and applicable individual subject PK parameters will be listed and summarized using descriptive statistics by treatment. 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. 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:

- Individual subject concentration data and summary statistics

- Individual subject plasma PK parameters and summary statistics

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

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)

- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Mean and median postdose concentration values that are ≤ LLOQ 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. Individual data on determination of plasma half-life and corresponding regression correlation coefficient will also be listed.

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.

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

8.3.2.   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.

8.3.3.   Changes from Protocol-Specified PK Analyses

The secondary endpoint of the correlation between C_t (concentration at Day 10) of LEN (Part A) and the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from baseline through Day 10 will be replaced CCI

CCI

9.   REFERENCES

No references were used in this document.

10.   SOFTWARE

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

Phoenix WinNonlin® 7.0 Pharsight 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,h]	Day 2	Day 3[h]	Day 4	CCI	Day 7[h]	Day 8	Day 9	Day 10[h]	Day 14	Day 29	Day 43	Day 57	Day 85[h]	Day 113	Day 141	Day 169[h]	Day 197	Day 225[h]	Early Termination
Written Informed Consent	X																				
Medical History	X																				
Complete Physical Examination	X	X																			X
Symptom Directed Physical Examination			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[j] (including weight)	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG	X	X	X								X	X		X	X			X		X	
Height	X																				
Hematology[f]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[g]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Estimated GFR[c]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and Urine Chemistry[k]	X	X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Urine Storage Sample		X		X			X			X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X											X		X	X	X	X	X	X	X	X
Serum FSH[i]	X																				
Urine Pregnancy test		X																			
HBV, HCV Testing	X																				
CD4+ Cell Count	X	X								X		X	X	X	X	X	X	X	X	X	X
HIV 1 Genotyping/ Phenotyping	X																				

	Screening[a]	Day 1[b,h]	Day 2	Day 3[h]	Day 4	CCI	Day 7[h]	Day 8	Day 9	Day 10[h]	Day 14	Day 29	Day 43	Day 57	Day 85[h]	Day 113	Day 141	Day 169[h]	Day 197	Day 225[h]	Early Termination
HIV 1 capsid Genotype/Phenotype[r]	X									X											
HIV DNA genotyping															X			X		X	
Plasma HIV 1 RNA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intensive PK Plasma Collection (Part A)		X[l]																			
Single Anytime PK Plasma Sample (Part A)[n]				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Plasma Sample (Part B)[o]		X	X	X	X		X	X	X	X											
PBMC PK Samples (Part B)[p]		X	X	X	X		X	X	X	X											
CCI																					
LEN Administration (Part A)		X																			
TAF Administration (Part B)		X																			
B/F/TAF dispensation										X			X		X		X		X		
Adverse Events/ Concomitant Meds	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a   Screening evaluations must be completed within 42 days prior to Day 1.

b   Day 1 tests and procedures must be completed prior to administration of the dose of study drug

c   According to the Cockcroft Gault formula

d   Within 72 hours of permanently discontinuing study. Counsel subject regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility.

e   Females of childbearing potential only

f   Hematology: CBC with differential and platelet count

g   Chemistries: Alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing if total amylase > 1.5 × ULN).

h   Fasting overnight (≥ 6 hours) required for Days 1, 3, 7, 10, 85, 169 and 225

i   FSH test is required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

j   Vital signs   blood pressure, pulse, respiration rate, and temperature, weight

k   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

l   Part A: Serial blood samples to determine pharmacokinetics (PK) in plasma will be collected at the following time points relative to study drug dosing 0 (pre dose), 1, 2,4, 8, 12 and 24 hours post dose.

n   Part A: Single Anytime PK sample to be collected at the Day 3, 4, and 7 through 225 visits.

o   Part B: Plasma PK samples to be collected at the following time points relative to study drug dosing: 0 (pre dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 hours post dose; as well as at Days 4, CCI 7, 8, 9 and 10 at approximately the same time in the morning as pre dose on Day 1.

p   Part B: PBMC PK samples to be collected at the following time points relative to study drug dosing: 0 (pre dose), 1, 2, 4, 6, 8, 12, 24 and 48 hours post dose, as well as at Days 4, CCI 7, 8, 9 and 10 at approximately the same time in the morning as pre dose on Day 1.

r   Part A: subjects require the HIV 1 capsid genotype/phenotype to confirm eligibility prior to randomization. Part B: the capsid genotype/phenotype will be completed for informational purposes, but it is not be required to confirm eligibility.

Appendix 2.   Determining Missing and Virtual visits due to COVID-19

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If a visit which was to be conducted in-person was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Appendix Table 1) and "Virtual" (or synonyms, see Appendix Table 1). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

STEP 1: Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Appendix Table 2.

STEP 2: Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (Computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

    i.   If Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL   1, else COVIDFL   0

    ii.   If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL   1, else VIRTFL   0

STEP 3: For any comments with COVIDFL   1, assign "Missed visit" or "Virtual visit as follows

    i.   IF COVIDFL   1 and the visit date is missing then result is 'Missed Visit'

    ii.   IF COVIDFL   1 and VIRTFL   1 then result is   'Virtual Visit'

    iii.   Otherwise result is missing

Appendix Table 1.   Examples of search terms for "COVID-19" and "Virtual" used to identify missed and virtual visits.

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

Appendix Table 2. **Examples of extraneous text terms to eliminate from the comment fields.**

a	down	in	she'd	until
about	during	into	she'll	up
above	each	is	she's	very
after	few	it	should	was
again	for	its	so	we
against	from	it's	some	we'd
all	further	itself	such	we'll
am	had	i've	than	were
an	has	let's	that	we're
and	have	me	that's	we've
any	having	more	the	what
are	he	most	their	what's
as	he'd	my	theirs	when
at	he'll	myself	them	when's
be	her	nor	themselves	where
because	here	of	then	where's
been	here's	on	there	which
before	hers	once	there's	while
being	herself	only	these	who
below	he's	or	they	whom
between	him	other	they'd	who's
both	himself	ought	they'll	why
but	his	our	they're	why's
by	how	ours	they've	with
could	how's	ourselves	this	would
did	i	out	those	you
do	i'd	over	through	you'd
does	if	own	to	you'll
doing	i'll	same	too	your
down	i'm	she	under	you're
	you've	yourself	yourselves	yours

Appendix 3.   Programming Specifications

1) For subjects who have previously screen failed, rescreened then enrolled into the study, the later date of rescreening will be used as the screening date. For subjects who have screen failed twice, the first screening date will be used as the screening date.

2) For enrolled subjects who have previously screen failed then rescreened, only eligibility criteria deviations from the rescreening visit were summarized in table and listings.

3) 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.

4) Please note, "Not Permitted", "Unknown", or missing categories will be excluded for percentage calculation. An exception is for Mode of infection (HIV Risk Factors), where "Unknown" will be included for percentage calculation, since a subject may fit more than 1 HIV risk factor, therefore percentage may add to more than 100%.

5) Graded Laboratory Abnormalities Summary

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	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)

6) PK concentration analysis visit names will follow day/hour labeling combinations defined in the protocol Section 6.6.1 (i.e. Day 1 48 hours post dose).

7) 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.

8) PK parameters at the individual subject level should be displayed with the following reported decimal places

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

t1/2, Tlast, Tmax, BEGHOUR and ENDHOUR: 2 decimal places

$AUC_{0\ D10}$, AUCtau, AUClast, AUCinf, %AUCexp, Vz/F, CL/F, CLss/F, Cmax, Clast, Ctau, AR_AUC, and AR_Cmax: 1 decimal place

NPOINTS: 0 decimal places

9) 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.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	15-Sep-2020 18:28:29
PPD	Clinical Research eSigned	16-Sep-2020 03:04:46
PPD	Clinical Pharmacology eSigned	17-Sep-2020 16:17:12