STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a 2-NRTI-Containing Regimen
Name of Test Drug:	Emtricitabine/Tenofovir Alafenamide (F/TAF; Descovy®)
Study Number:	GS-US-311-1269
Protocol Version (Date):	Amendment 2 (02 August 2017); South Africa Amendment 2.1 (10 August 2017); UK Addendum 2.0 (15 August 2017)
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1,25-OH vitamin D	1,25-dihydroxy vitamin D
25-OH vitamin D	25-hydroxy vitamin D
ABC/3TC	abacavir/lamivudine
AE	adverse event
AIDS	acquired immuno deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
BsAP	bone-specific alkaline phosphatase
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CSR	clinical study report
CTX	C-type collagen sequence
DMC	data monitoring committee
DOB	date of birth
DRV	darunavir
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
FAS	Full Analysis Set
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC or F	emtricitabine
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus (type 1)
HLGT	high-level group term

HLT	high-level term
IPK	intensive pharmacokinetic(s)
IRT	interactive response technology
LDL	low-density lipoprotein
LLT	lower-level term
LOQ	limit of quantitation
M = E	missing = excluded
M = F	missing = failure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search term
NLP	natural language processing
NRTI	nucleoside reverse transcriptase inhibitor
OLE	open-label extension
P1NP	procollagen type I N-terminal propeptide
PI	protease inhibitor
PK	pharmacokinetic(s)
PBMC	peripheral blood mononuclear cell
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily
RBC	red blood cell
RBP	retinol-binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide (Vemlidy®)
TBLH	total body less head
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV, TFV-DP	tenofovir, tenofovir-diphosphate
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{tau}	area under the plasma drug concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable plasma drug concentration
C_{max}	maximum observed plasma drug concentration
C_{tau}	observed plasma drug concentration at the end of the dosing interval
CL/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
V_z	volume of distribution

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 final clinical study report (CSR) for Study GS-US-311-1269. This SAP is based on study protocol amendment 2 (dated 02 August 2017), South Africa amendment 2.1 (dated 10 August 2017), UK addendum 2.0 (dated 15 August 2017), 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.

1.1. Study Objectives and Endpoints

The primary objectives of this study are:

- To evaluate the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and confirm the TAF dose in HIV-1 infected children and adolescents virologically suppressed on a 2 nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-containing regimen
- To evaluate the safety, tolerability of F/TAF through Week 24

The primary endpoints are:

- The PK parameter AUC_{tau} for TAF
- Incidence of treatment-emergent serious adverse events (SAEs) and all treatment-emergent adverse events (TEAEs) through Week 24

The secondary objectives are:

- To evaluate the PK of TFV and FTC
- To evaluate the safety, tolerability, and efficacy of F/TAF through Week 48

The secondary endpoints are:

- PK parameters C_{max}, C_{last}, CL/F, and Vz /F for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC and TFV
- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events through Week 48
- The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count (cells/µL) and CD4 percentage at Weeks 24 and 48
- The palatability and acceptability of the age-appropriate F/TAF formulation

The tertiary endpoints are:

- The percentage change from baseline in spine and total-body-less-head (TBLH) bone mineral density (BMD) at Weeks 24 and 48
- The percentage change from baseline in bone safety tests at Weeks 12, 24, and 48
- The percentage change from baseline in renal safety tests at Weeks 12, 24, and 48

1.2. Study Design

This is an open-label, multicohort switch study to evaluate the PK, safety, and efficacy of F/TAF in HIV-1 infected children (1 month to < 12 years) and adolescents (12 to < 18 years) who are virologically suppressed (HIV-1 RNA <50 copies/mL for at least 6 consecutive months) on a stable 2-NRTI-containing regimen.

A minimum of 100 children and adolescent participants, 1 month to < 18 years of age of either sex, were planned to be enrolled to receive F/TAF. The study was planned to proceed in sequential cohorts as follows:

Cohort 1 (Adolescents 12 to < 18 years, ≥ 35 kg):

All participants in Cohort 1 (n = 25) switched their current 2-NRTI-containing regimen to open-label F/TAF while continuing on their third antiretroviral (ARV) agent through 48 weeks. An intensive PK (IPK) evaluation was conducted at the Week 2 visit to confirm the dose of TAF and to characterize TFV and FTC exposures. Following completion of the Week 2 IPK visit, all participants continued to receive F/TAF plus their third ARV agent and returned for study visits through Week 48.

Cohort 2:

Participants in Cohort 2 had to be on a boosted protease inhibitor (PI) or any other 3rd ARV agent and switched their current 2-NRTI-containing regimen to open-label F/TAF while continuing their boosted PI or 3rd agent through 48 weeks.

Cohort 2 planned to enroll by treatment group into a 2-part study (Parts A and B). Table 1-1 listed Part A as below.

Part A

Table 1-1. Cohort 2 Part A

Cohort 2	Age Range	Weight Range at Screening	Number of Participants		
			ATV + F/TAF	LPV or DRV + F/TAF	Other third ARV Agent + F/TAF
Group 1	6 to 12 years	25 kg	n 10	n 6	n/a
Group 2 (participants able to swallow a tablet)	2 to < 12 years	17 kg to < 25 kg	n ≥ 10	n ≥ 7	

All participants in Part A underwent an IPK evaluation at either the Week 2 or Week 4 visit (+7 days) to confirm the dose of TAF and to characterize the exposure of TFV. Following completion of the IPK visit, all participants continued to receive F/TAF plus their third ARV agent and returned for study visits through Week 48.

Part B

After confirmation of TAF dose in Part A, approximately 10 additional participants were planned to be enrolled in Part B, to receive F/TAF while continuing their third ARV agent through 48 weeks.

Enrollment into the study has concluded and only Part A was enrolled. With the introduction of F/TAF to Study GS-US-216-0128 via Study GS-US-216-0128 protocol amendment 7, participants in this study could roll over to GS-US-216-0128 and no further enrollment in this study was required. This meant that planned Cohort 2 Part B for this study was not opened for enrollment and no further participants were enrolled into Cohort 2 Part A. Details can be found in Section 2.6.

Cohort 3 and 4

The details of Cohort 3 and 4 are in Section 3.2.2 of study protocol amendment 2. The enrollment of Cohort 3 and 4 were not initiated due to study enrollment pause (as in Cohort 2 Part B above). Additional details can be found in Section 2.6.

Study Procedure/Frequency:

At screening, HBV and HCV serology were analyzed.

At the Screening, Baseline/Day 1, and all subsequent study visits, vital signs, weight and height/length, laboratory analyses (hematology, chemistry, and urinalysis), plasma HIV-1 RNA, CD4 cell count, complete or symptom directed physical examinations, and eGFR using the Schwartz formula were performed. Serum (screening) or urine (all other visits) pregnancy tests were performed on female participants of childbearing potential.

Participants returned for study visits at Weeks 1, 2, 4, 8, 12, 24, 36, and 48. After completion of 48 weeks of treatment in the study, all eligible participants were given the option to participate in an extension phase of the study in which visits occurred every 12 weeks. Adverse events and concomitant medications were assessed at each visit.

Tanner stage assessments were performed for participants ≥ 6 years of age at the time of the visit at Baseline/Day 1, Weeks 24, 48, and every 12 weeks thereafter, or until participants reached Tanner Stage 5, after which point Tanner assessments were no longer performed.

Dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body were performed at Baseline/Day 1, Weeks 24 and 48, and every 24 weeks thereafter to measure spine BMD and TBLH BMD.

Serum was collected for bone safety tests (collected fasted), including bone specific alkaline phosphatase (BsAP), serum phosphorus, procollagen type I N-terminal propeptide (P1NP), C-type collagen sequence (CTX), parathyroid hormone (PTH), 1,25-OH vitamin D, and 25-OH vitamin D. The assessment schedules differed for different cohorts:

- Cohort 1 only: Baseline/Day 1, Weeks 4, 12, 24 and 48, and every 24 weeks thereafter.
- Cohort 2: Baseline/Day 1, Weeks 8, 12, 24 and 48, and every 24 weeks thereafter.

For both cohorts, urine was collected for urine chemistry and selected renal safety tests, including retinol binding protein and beta-2-microglobulin, at Baseline/Day 1, Weeks 2, 4, 8, 12, 24 and 48, and every 12 weeks thereafter.

For Cohorts 1 and 2 (both groups), metabolic assessments were collected for fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) at Baseline/Day 1, Weeks 24 and 48, and every 24 weeks (±10 days) thereafter.

For PK sampling:

- Single PK samples were collected for both cohorts
  - Weeks 1 and 24: a single random PK sample.
  - Weeks 4 and 12: a single observed dosing PK sample at any time between 15 minutes to 4 hours post dose. (Note: for Cohort 2 Part A, a single observed dosing PK sample did not need to be collected at Week 4 if IPK was also collected at the Week 4 visit)
- Week 8: a trough sample at 0 hours (predose, ≤ 30 minutes prior to dosing) at Week 8.
- Intensive PK (IPK) sampling
  - Cohort 1 participated in an IPK evaluation at the Week 2 visit as detailed in the PK manual.
  - Cohort 2 Part A participated in an IPK evaluation during either the Week 2 or Week 4 visit or within 7 days after the completion of Week 2 or Week 4 visit as detailed in the PK manual.

Peripheral blood mononuclear cell (PBMC) collection was performed at study sites that could perform PBMC processing.

- Cohorts 1 and 2: PBMC collection was performed at the Week 8 visit.

Palatability and Acceptability Assessment:

- Cohort 1: At the Week 2 visit, palatability and acceptability were assessed 30 to 60 minutes after study drug dosing for all participants undergoing IPK sampling. Acceptability was also assessed 30 to 60 minutes after study drug dosing for active participants at the next study visit.

- Cohort 2 Part A: Palatability and acceptability were assessed at the Week 2 or Week 4 visit, or within 7 days after the completion of the Week 2 or Week 4 visit, 30 to 60 minutes after study drug dosing for all participants undergoing IPK sampling.

Participants who prematurely discontinued from the study or did not participate in the extension phase were required to return to the clinic for a 30-Day Follow-up Visit.

Additional details of scheduled assessments can be found in Section 12.1.

1.3. Sample Size and Power

Cohort 1: Twenty-five participants from Cohort 1 in the TAF treatment group were anticipated to provide at least 90% power to target a 95% confidence interval (CI) within 60% and 140% of the geometric mean estimate of apparent CL and apparent V_z of TAF, assuming a standard deviation (SD) of 0.60 for CL and 0.58 for Vz (natural log scale) estimated from Study GS-US-292-0106 Cohort 1 Part A.

Cohort 2 (Group 1) Part A: At least 10 participants on boosted ATV + F/TAF and 6 participants on boosted LPV or DRV + F/TAF, compared with the population PK (PopPK) data from 44 adult participants on boosted ATV + F/TAF and 87 adult participants on boosted LPV or DRV + F/TAF in Study GS-US-311-1089, respectively, each was anticipated to provide at least 80% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric participants vs. adult participants) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratios of TAF AUC_{tau} between pediatric participants and adult participants are equal to 1 and the SDs are 0.40 (with boosted ATV + F/TAF) and 0.33 (with boosted LPV or DRV + F/TAF) ng·h/mL for TAF AUC_{tau} (natural log scale) estimated from the PopPK data in Study GS-US-311-1089.

Part A of Cohorts 2 (Group 2), 3, and 4: At least 10 participants on boosted ATV + F/TAF and 7 participants on any other third agent + F/TAF in each group or cohort, compared with the PopPK data from the 292 adults on any third agent + DVY in Study GS-US-311-1089, were anticipated to provide 90% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric participants vs. adult participants) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratio of TAF AUC_{tau} between pediatric participants and adult participants is equal to 1, and the SD is 0.48 ng·h/mL for TAF AUC_{tau} (natural log scale) estimated from the PopPK data in Study GS-US-311-1089.

Initially, a total of at least 100 participants receiving F/TAF from Cohort 1, and Parts A and B of Cohort 2 (Groups 1 and 2), Cohort 3, and Cohort 4 combined were anticipated to provide

reasonable assessment of safety through Week 48 in pediatric participants. However, Cohort 2 Part B, Cohort 3 and 4 were not enrolled, and details can be found in Section 2.6.

Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 7.0) and R.

2. TYPE OF PLANNED ANALYSIS

2.1. Cohort 1 Week 48 Interim Analysis

A Cohort 1 Week 48 analysis was planned to be conducted after all participants in Cohort 1 had either completed their Week 48 visit or prematurely discontinued study drug.

This analysis was not performed. The results for Cohort 1 through Week 48 were later included as part of the Interim Analysis 2 CSR.

2.2. Cohort 2 Week 24 Interim Analysis

A Cohort 2 Week 24 analysis was planned to be conducted after all participants in Cohort 2 had either completed their Week 24 visit or prematurely discontinued study drug.

This analysis was not performed. The results for Cohort 2 Part A (Groups 1 and 2) through Week 24 were later included as part of the Interim Analysis 2 CSR.

2.3. Interim 2 Analysis

This analysis included data from Cohort 1 and Cohort 2 Part A (Groups 1 and 2). It was conducted after participants enrolled in Cohort 1 and Cohort 2 Part A (Groups 1 and 2) had completed their Week 48 visit or prematurely discontinued study drug.

2.4. Final Analysis

The final analysis will be performed after all participants (ie, participants in Cohort 1 and Cohort 2 Part A [Groups 1 and 2]) have completed the study or prematurely discontinued, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

2.5. Data Monitoring Committee (DMC) Analyses

An external multidisciplinary Data Monitoring Committee (DMC) was planned to review the progress of the study and perform interim reviews of the safety data in order to protect participant welfare and preserve study integrity.

DMC review was not performed for the study.

2.6. Changes From Protocol-Specified Planned Analyses

With the introduction of F/TAF to Study GS-US-216-0128 via the Study GS-US-216-0128 protocol amendment 7, it was agreed that participants in Study GS-US-311-1269 could roll over to GS-US-216-0128 and no further enrollment in this study was required. This meant that Cohorts 2 Part B, 3, and 4 for this study were not opened for enrollment and no further participants were enrolled into Cohort 2 Part A. The enrollment was closed, and the last participant was enrolled on 22-May-2019.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

3.1. Analysis Sets

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

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by cohort (and group, where applicable) and overall.

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

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set will include all participants who are enrolled into the study (ie, received a study participant identification number in the study after screening).

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) will include all enrolled participants who received at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set will include all enrolled participants who received at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.4. DXA Analysis Set

3.1.4.1. Total Body Less Head DXA Analysis Set

The TBLH DXA Analysis Set will include all participants who are enrolled and have received at least 1 dose of study drug and have a nonmissing TBLH BMD value at the baseline visit.

3.1.4.2. Spine DXA Analysis Set

CCI [redacted].

3.1.5. Pharmacokinetic Analysis Set

3.1.5.1. IPK Analysis Set

The IPK Analysis Set will include all participants who enrolled in Cohort 1 or Part A of Cohort 2 (each group) for IPK evaluation and received at least one dose of study medication and have at least 1 nonmissing PK concentration data for any analyte of interest (eg, FTC, TAF, and TFV). The IPK analysis set is used for analyses of IPK analytes of TAF, TFV, and FTC.

3.1.5.2. PK Analysis Set

The PK Analysis Set will include all participants who are enrolled and have received at least one dose of study drug and have at least 1 nonmissing PK concentration data for any analyte of interest (ie, FTC, TAF, and TFV). The PK analysis set is used for analyses of general PK.

3.1.5.3. PBMC PK Analysis Set

The PBMC PK analysis set will include all participants who are enrolled and have received at least one dose of study medication and have at least 1 nonmissing concentration data of TFV-DP. The PBMC PK analysis set will be used for PK analyses of TFV-DP.

3.2. Participant Grouping

Participants will be analyzed based on the cohort (and group, if applicable) to which they were initially assigned as well as overall.

For the PK Analysis Set, participants will be grouped according to the actual treatment they received.

Participants will be grouped into the following:

- Cohort 1: Age 12 to <18 years and weight ≥ 35 kg
- Cohort 2 Group 1: Age 6 to < 12 years and weight ≥ 25 kg
- Cohort 2 Group 2: Age 2 to < 12 years and weight 17 to < 25 kg

3.3. Strata and Covariates

This is not a randomized study. Therefore, a stratified randomization schedule is not applicable when enrolling participants. No covariates will be included in efficacy or safety analyses.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this 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.

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE start is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.6.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at start 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 (other than HIV-1 RNA) that are continuous in nature but 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 as 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 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).

HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes.

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.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug 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.

Last Dose Date is the earliest of the last dosing dates of F/TAF and the third agent in a participant's study regimen.

For F/TAF, the last dosing date is the latest nonmissing end date recorded on the Study Drug Administration eCRF with "Study Drug Permanently Withdrawn" box checked for participants who prematurely discontinued study drug, or who completed study drug according to the Study Drug Completion eCRF (or Study Drug Completion (Post-Week 48 Extension Phase) eCRF if applicable). If the date of last dose is missing (eg, due to lost to follow-up) for participants who prematurely discontinued study drug, the latest of nonmissing study drug start dates and end dates, the clinic visit dates, laboratory visit dates and vital signs assessments dates excluding the date of the 30-day follow-up visit will be used to impute the last dosing date. For other partial missing last dose date, please see the Appendix 12.4 for imputation rule details.

The third agent in a participant's existing treatment regimen is the ARV medication (excluding abacavir (ABC) and lamivudine (3TC)) that a participant was taking immediately prior to the first dose date (ie, ARV start date before the first dose date of study drug and ARV end date after the first dose date of study drug minus 1). The last dosing date of the third agent is recorded on the Non-Study ARV Medication eCRF. If the third agent is ongoing, then the last dose date of the study regimen will be the last dosing date of F/TAF.

For an ARV which is marked as current but not ongoing on the Non-Study ARV Medication eCRF, if the ARV end date is missing (eg, due to lost to follow-up), the latest of nonmissing study drug start date and end date, the clinic visit dates, and laboratory visit dates excluding the date of the 30 day follow-up visit will be used to impute the end date of the ARV.

Last Study Date is the latest of the nonmissing study drug start dates, study drug end dates, and the clinic visit, and laboratory visit dates, including the 30-day follow-up visit date for participants who a) prematurely discontinued study from main phase or b) completed study in the main phase but did not participate in the extension phase according to the Study Completion eCRF or c) discontinued study from the extension phase according to the Study Completion eCRF.

Baseline value is defined as the last nonmissing value obtained on or prior to Study Day 1 for all assessments, except for the BMD data, which is the last nonmissing value obtained prior to or up to Study Day 21 (inclusive).

3.8.2. Analysis Visit Windows

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

The analysis windows for HIV-1 RNA, CD4 cell count, CD4 %, hematology, chemistry, and urinalysis laboratory tests, $eGFR_{Schwartz}$, vital signs, height, and weight are presented in Table 3-1 below.

Table 3-1. Analysis Visit Windows for HIV-1 RNA, CD4 cell count, CD4 %, Hematology, Chemistry, and Urinalysis Laboratory Tests, $eGFR_{Schwartz}$, Vital Signs, Height, and Weight

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	10
Week 2	14	11	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
CCI			
CCI			

Hematology profile includes complete blood count (CBC) (hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit, mean corpuscular volume (MCV), red blood cells (RBC) and white blood cells (WBC) with differential (absolute basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet count.
Chemistry profile includes albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct and indirect bilirubin, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium (albumin corrected), chloride, creatine kinase, serum glucose, serum creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase, and lipase.
Vital signs includes blood pressure, temperature, heart rate, and respiration rate.
Urinalysis does not include urine chemistry and urine renal safety.

The analysis windows for fasting glucose, urine chemistry and urine renal safety tests are presented in Table 3-2 below.

Table 3-2. Analysis Visit Windows for Fasting Glucose, Urine Chemistry and Urine Renal Safety Tests[a]

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	252
Week 48	336	253	378
CCI			

a Urine chemistry tests include creatinine, phosphate, uric acid, albumin, calcium, magnesium, protein, N-telopeptide and N-telopeptide/creatinine; Urine renal safety tests (collected fasted) include retinol binding protein (RBP), beta-2-microglobulin, urine RBP to urine creatinine ratio, urine beta-2-microglobulin to urine creatinine ratio, and urine protein to creatinine ratio.

The analysis windows for metabolic and BMD assessments are presented in Table 3-3 below.

Table 3-3. Analysis Visit Windows for Metabolic Assessments[a] and BMD Assessments

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	420
CCI			

a Metabolic assessments include lipid panel (total cholesterol, high-density lipoprotein [HDL], direct low-density lipoprotein [LDL], and triglycerides).

The analysis windows for serum bone safety assessments for Cohort 1 are presented in Table 3-4 below.

Table 3-4. Analysis Visit Windows for Cohort 1 Serum Bone Safety Assessments[a]

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	252
Week 48	336	253	420
CCI			

a Bone safety tests (collected fasted) include bone specific alkaline phosphatase (BsAP), P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D.

The analysis windows for serum bone safety assessments for Cohort 2 are presented in Table 3-5 below.

Table 3-5. Analysis Visit Windows for Cohort 2 Serum Bone Safety Assessments[a]

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 8	56	2	70
Week 12	84	71	126
Week 24	168	127	252
Week 48	336	253	420
CCI			

a Bone safety tests (collected fasted) include bone specific alkaline phosphatase (BsAP), P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D.

The analysis windows for 12-lead Electrocardiogram (ECG) are presented in Table 3-6 below.

Table 3-6. Analysis Visit Windows for 12-lead ECG

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
CCI			

The analysis windows for Tanner Stage assessments are presented in Table 3-7 below.

Table 3-7. Analysis Visit Windows for Tanner Stage Assessments

Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	378
CCI			

For Tanner stage, assessment is performed for participants ≥ 6 years of age at the time of the visit at Baseline/Day 1, Weeks 24 and 48, and every 12 weeks thereafter, or until participants reach Tanner Stage 5.

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 dosing 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, or the measurement with the lowest severity (eg, normal

will be selected over abnormal for safety ECG findings) for categorical data. The exception is for HIV-1 RNA (see below).

- For postbaseline visits:

- For CD4 cell count and CD4% data, the record(s) collected on the latest day in the window will be selected for analysis.

- For DXA data, including spine or TBLH BMD bone loss where bone loss is ≥ 4% from baseline, a repeat measurement is to be taken to confirm the result (bone loss repeat visit). For repeat results, the latest measurement (ie, the bone loss repeat visit) will be selected for analysis. In addition, it should be noted that some parameters at a visit will have two measurements and others for the same participant will only have one.

- For other numeric observations (ie, except HIV-1 RNA, CD4 cell count, CD4%, spine or TBLH BMD where a bone loss repeat visit occurs), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

    - For any numeric observations except HIV-1 RNA, if there are multiple records on the selected day, the average will be taken. For categorical observations, if there are multiple records within an analysis window, the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are two days equidistant from the nominal day, the later day will be selected. If there are multiple records on the selected day, the worst severity will be taken.

- 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" or "COBAS 6800" 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 date/time, the results from the "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple: "HIV RNA Taqman 2.0" or "COBAS 6800" records with the same collection date/time, the geometric mean will be taken for analysis purposes.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant enrolled, last participant enrolled and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided for each country, and investigator within the country, by cohort (and group, where applicable) and overall. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A summary of participant disposition will be provided by cohort (and group, where applicable) and overall. This summary will present the number of participants screened, screened participants who were not enrolled, including those screen failed, and who met all eligibility criteria but were not enrolled, participants enrolled, participants enrolled but never treated, and participants in each of the categories listed below:

- Safety Analysis Set
- FAS
- For the 48-week treatment phase:
  - Completed study drug
  - Prematurely discontinued study drug prior to Week 48 with reasons for premature discontinuation of study drug
  - Completed study
  - Prematurely discontinued the study prior to Week 48 with reasons for premature discontinuation of study
- For the extension phase:
  - Entered the extension phase
  - Completed study drug in the extension phase
  - Prematurely discontinued study drug in the extension phase with reasons for premature discontinuation of study drug
  - Completed study in the extension phase
  - Prematurely discontinued from the study in the extension phase with reasons for discontinuation

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation in the main phase will be the total number of participants in the Safety Analysis Set corresponding to that column. The denominator for the percentage calculation in the extension phase will be the total number of participants entering extension phase corresponding to that column.

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

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

- Enrollment information, including cohort, treatment group, date of informed consent signed, enrollment protocol version, country, and if they have met all eligibility criteria.
- Screen failures, with reasons for screen failure (will be provided by screening ID number in ascending order)
- Participant disposition, including cohort, third agent, treatment group, date of enrollment, first dose date, last dose date and day, end of study date and day, study drug discontinuation and study discontinuation for the main phase and their corresponding reasons, if entered extension phase, study drug discontinuation and study discontinuation for the extension phase and their corresponding reasons.
- Participant profiles, including cohort, treatment group, date of enrollment, first dose date, last dose date and day, last visit date and day, last laboratory date and day, and last study date and day.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, refer to Section 3.8.1 for imputation method.

The total duration of exposure to study drug will be summarized using descriptive statistics, and using the number (ie, cumulative counts) and percentage of participants exposed through the following time periods: ≥ 1 Week (7 days), ≥ 2 weeks (14 days), ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), and every 12 weeks (84 days) thereafter.

Summaries will be provided by cohort (and group, where applicable) and overall for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

Study drug adherence is calculated based on tablet counts. The presumed total number of tablets administered to a participant is determined by the data collected on the Study Drug Accountability eCRF. Adherence (%) to the study drug will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{\text{Number of tablets taken}}{\text{Number of tablets prescribed}}$$

$$= 100 \times \frac{\text{Sum of number of tablets taken at each dispensing period [1]}}{\text{Sum of number of tablets prescribed at each dispensing period [2]}}$$

[1] **Number of tablets taken at each distinct dispensing period** is calculated as the minimum of a) the daily number of tablets prescribed multiplied by the **duration of treatment at each dispensing period**, and b) number of tablets taken (number of tablets dispensed minus the number of tablets returned). Total number of tablets taken is determined by summing the number of tablets taken from all evaluable dispensing periods.

[2] **Number of tablets prescribed at each distinct dispensing period** is calculated as the daily number of tablets prescribed multiplied by the **duration of treatment at each dispensing period**. Total number of tablets prescribed is determined by summing the number of tablets prescribed from all evaluable dispensing periods.

The duration of treatment at each dispensing period is calculated as the minimum of (a) the last returned date of the same dispensing period, (b) the date of permanent discontinuation of study drug, and (c) next study drug dispensing date, minus the dispensing date of the study drug.

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

For a record where the number of tablets returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of tablets returned was 0. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, all records for the same dispensing date will be excluded from both denominator and numerator calculations.

Treatment adherence will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug.

Descriptive statistics by cohort (and group, where applicable) and overall for treatment adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to treatment adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for participants who return at least 1 bottle and have calculable treatment adherence during the study using the Safety Analysis Set.

No formal statistical testing is planned.

Drug accountability and treatment adherence data will be listed.

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

4.3. Protocol Deviations

Participants 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 participants who did not meet at least 1 eligibility criterion by cohort (and group, where applicable) and overall, based on the All Enrolled Analysis Set.

A by-participant listing will be provided for those participants 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 participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with at least 1 important protocol deviation will be summarized by cohort (and group, where applicable) and overall as well as by deviation category for the All Enrolled Analysis Set. Additionally, the number and percentage of participants with at least 1, 2, or 3 or more important protocol deviations will be summarized. The total number of important protocol deviations will be summarized by deviation category.

A by-participant listing will be provided for those participants with protocol deviations, including a column specifying whether the protocol deviation is important.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis. Please refer to Appendix 12.2 for data collection and determination of COVID-19 impact Data.

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

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A summary of important protocol deviations due to COVID-19 will be provided, similar to the summary described in the protocol deviations section (Section 4.3).

The number and percentage of participants with nonimportant protocol deviations related to COVID-19 by number of deviations (eg, at least 1, with 1, 2, 3 or more deviations) will be summarized by cohort (and group, where applicable) and overall.

A by-participant listing will be provided for participants with important and nonimportant protocol deviations related to COVID-19 separately, if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

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

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 12.2.2.

4.4.4. Adverse Events Due to COVID-19

Adverse events of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 Standardized MedDRA Query (SMQ) narrow search from standardized Medical Dictionary for Regulatory Activities (MedDRA) query. A by-participant listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, age group, sex at birth, race, and ethnicity) and baseline characteristics (body weight [in kg], body weight Z-score, height [in cm], height Z-score, body mass index [BMI; in kg/m^2], BMI Z-score, body surface area [in m^2], and Tanner stage) will be summarized by cohort (and group, where applicable) and overall using descriptive statistics for continuous variables, and using number and percentage of participants for categorical variables. Additionally, Tanner Stage will be summarized separately for gender (breasts and pubic hair for female; genitalia and pubic hair for male). The maximum Tanner Stage will be summarized for each gender separately.

The summary of demographic data will be provided for the Safety Analysis Set. Missing values (including not permitted) will not be included in the denominator when calculating percentages.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Third agent in a participant's pre-existing treatment regimen: (a) ATV + RTV, (b) COBI + DRV, (c) DRV + RTV, (d) DTG, (e) EFV, and (f) LPV/r
- HIV-1 RNA categories (copies/mL): (a) < 50, and (b) ≥ 50
- CD4 cell count (cells/µL)
- CD4 cell count categories (cells/µL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Years diagnosed with HIV (calculated as time prior to first dose date)
- Mode of infection (HIV risk factor): (a) Heterosexual Sex, (b) Homosexual Sex, (c) IV Drug Use, (d) Transfusion, (e) Vertical Transmission, (f) Other, and (g) Unknown
- HIV disease status: (a) AIDS, (b) Asymptomatic, (c) Symptomatic HIV Infection, and (d) Unknown
- HBV surface antigen: (a) Negative, and (b) Positive

- HBV surface antibody: (a) Negative, and (b) Positive
- HCV antibody: (a) Negative, and (b) Positive
- eGFR calculated using the Schwartz Formula (mL/min/1.73m^2)
- Proteinuria by urinalysis (dipstick): (a) Grade 0, (b) Grade 1, (c) Grade 2, and (d) Grade 3

These baseline characteristics will be summarized by cohort (and group, where applicable) and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

5.3. Medical History

Medical history will be collected at screening for HIV-1 disease-related events. Medical history will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

There is no primary efficacy endpoint in this study.

6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count (cells/μL) and CD4 percentage at Weeks 24 and 48

6.2.1. Definition of the Secondary Efficacy Endpoints

6.2.1.1. Percentage of Participants with HIV-1 RNA < 50 copies/mL at Week 24 as Determined by the US FDA-defined Snapshot Algorithm

The definition of above endpoint can be referred to in the Interim Analysis 2 SAP.

6.2.1.2. Percentage of Participants with HIV-1 RNA < 50 copies/mL at Week 48 as Determined by the US FDA-defined Snapshot Algorithm

The definition of above endpoint can be referred to in the Interim Analysis 2 SAP.

6.2.2. Analysis of Secondary Efficacy Endpoints

The FAS will be the primary analysis set for the secondary efficacy endpoints. No formal statistical testing is planned.

6.2.2.1. Percentage of Participants with HIV-1 RNA < 50 copies/mL at Week 24 as Determined by the US FDA-defined Snapshot Algorithm

All required analyses for this endpoint have already been reported as part of Interim Analysis 2.

6.2.2.2. Percentage of Participants with HIV-1 RNA < 50 copies/mL at Week 48 as Determined by the US FDA-defined Snapshot Algorithm

All required analyses for this endpoint have already been reported as part of Interim Analysis 2.

6.2.2.3. Change from Baseline in CD4 Cell Counts and Percentages

CD4 cell count and CD4% data will be summarized using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation or completion of study drug).

Absolute values and changes from baseline in CD4 cell count (cells/μL) and CD4% at each visit will be summarized by cohort (and group, where applicable) and overall and by visit descriptively (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and will also include the 95% CI based on the t-distribution.

The mean and 95% CI of change from baseline over time by cohort (and group, where applicable) and overall will be plotted.

The absolute values of CD4 cell count (cells/μL) and CD4% at each visit will also be listed.

CCI

6.4. Changes From Protocol-Specified Efficacy Analyses

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

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be 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 eCRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious AEs (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. Serious AEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as events that meet one of the following criteria:

- Any AEs with a start date on or after the date of the first dose of study drug and up to 30 days after the permanent discontinuation of the study drug
- Any AEs that result in permanent study drug discontinuation

7.1.5.2. Incomplete Dates

If the start date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of start determine whether an AE is treatment-emergent (TE). The event is considered TE if both of the following 2 criteria are met:

- The AE start date is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE start date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

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

7.1.6. Summaries of Adverse Events and Deaths

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

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by cohort (and group, where applicable) and overall. All deaths observed in the study will also be included in this summary.

In addition, a brief, high-level summary of TEAEs up to the nominal Week 24 visit will also be provided by cohort (and group, where applicable) and overall. Summaries of AEs up to nominal Week 24 will include any AE with start date on or before the nominal Week 24 visit date. The same analysis will be repeated for the nominal Week 48 visit.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, cohort (and group, where applicable), and overall as follows:

- TEAEs
- TEAEs with Grade 2 or higher
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 2 or higher
- TE treatment-related AEs with Grade 3 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 (ie, outcome of death)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC.

In addition, all TEAEs and TE treatment-related AEs will be summarized by PT only, in descending order of total frequency. All TEAEs up to nominal Week 24 visit and nominal Week 48 visit will also be summarized by PT only.

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

- All AEs, indicating whether the event is TE
- All AEs up to nominal Week 24 visit, indicating whether the event is TE
- All AEs up to nominal Week 48 visit, indicating whether the event is TE
- All AEs with severity of Grade 3 or higher
- All SAEs
- All treatment-related SAEs
- All deaths
- All AEs leading to premature discontinuation of study drug
- All AEs leading to death
- All AEs leading to premature discontinuation of study

7.1.6.2. Summaries of AE Incidence by Severity

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC and PT, by cohort (and group, where applicable) and overall.

- TEAEs by maximum severity
- TE treatment-related AEs by maximum severity

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

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Category C Events in HIV

On an ongoing basis AEs will be reviewed for events that might meet the definition of Category C events that are indicative of an acquired immune deficiency syndrome (AIDS)-defining diagnosis. The Gilead medical monitor will review possible Category C events and approve the events that meet the definition. Those events that do meet the Category C definition of an AIDS-defining diagnosis will be listed. A list of Category C AIDS-Defining Diagnosis can be found in Appendix 6 of study protocol amendment 2.

7.1.7.2. Fracture Events

Summaries of the following TEAEs of interest will be produced to enhance the analysis of safety data.

- AEs of fracture events, utilizing a MedDRA search term (MST) list developed by Gilead

The number and percentage of participants who had any of the above events will be summarized for each cohort (and group, where applicable) and overall by AE of interest category and PT. A by-participant listing of fracture events will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. 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.

Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to 30 days after permanent discontinuation of study drug.

A by-participant listing for laboratory test results will be provided by participant 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 will be flagged in the data listings, as appropriate.

A listing will present laboratory test reference ranges for hematology, serum chemistry (including liver-related and bone-related evaluations), urinalysis, CD4 cell count and percentage.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort (and group, where applicable) and overall for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline at each postbaseline analysis window (if specified)

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

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 draw are available and serum albumin value is < 4.0 g/dL.

- Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 x (4.0 - albumin [g/dL]).

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

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.

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

For triglycerides, LDL, and cholesterol, the protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without 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 time point during the time period specified in Section 7.2. 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 TE.

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

The following summaries (number and percentage of participants) for TE laboratory abnormalities will be provided by laboratory test and by cohort (and group, where applicable) and overall; participants will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Graded TE laboratory abnormalities
- Grade 3 or 4 TE laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the time period specified in Section 7.2.

A by-participant listing of graded laboratory abnormalities, as well as Grade 3 or 4 laboratory abnormalities will be provided by participant ID number and visit in chronological order. These listings will include all test results that were collected throughout the study for the laboratory test of interest, with all applicable severity grades displayed and TE laboratory abnormalities flagged.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after baseline will be examined and summarized using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- Alkaline phosphatase (ALP): > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- AST or ALT > 3 x ULN, total bilirubin > 2 x ULN, and ALP < 2 x ULN

The summary will include data from all postbaseline visits during the time period specified in Section 7.2. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of participants who met at least 1 of the above criteria will be provided.

Participants with AST or ALT > 3 x ULN, Total bilirubin > 1 x ULN, or ALP > 1.5 x ULN will also be listed.

7.2.4. Metabolic Laboratory Evaluations

For metabolic assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, direct LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized and listed based on the Safety Analysis Set.

7.2.5. Renal Safety Evaluations

7.2.5.1. Serum Creatinine and $eGFR_{Schwartz}$

The Schwartz formula will be used to calculate eGFR:

- eGFR ($mL/min/1.73m^2$) = $k \times L/S_{Cr}$, where k is the proportionality constant (0.55 for children [≥ 2 to < 12 years] and adolescent females ≥ 12 years; 0.70 for adolescent males ≥ 12 years, L is height (cm), SCr is serum creatinine (mg/dL)

Baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{Schwartz}$ will be summarized by cohort (and group, where applicable) and overall by visit using descriptive statistics.

Median (Q1, Q3) of the change from baseline values for serum creatinine and $eGFR_{Schwartz}$ will be plotted using a line plot by cohort (and group, where applicable), by analysis window.

7.2.5.2. Renal Safety Tests

Renal safety tests, including retinol binding protein (RBP), beta-2-microglobulin, urine creatinine, urine RBP to urine creatinine ratio, urine beta-2-microglobulin to urine creatinine ratio, and urine protein to creatinine ratio, will be summarized by visit using descriptive statistics and listed.

7.2.6. Bone Safety Evaluations

7.2.6.1. Bone Mineral Density

Bone mineral density data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of BMD data will be provided for the spine using the Spine DXA Analysis Set and TBLH using the TBLH DXA Analysis Set.

Descriptive statistics will be provided by cohort and overall and by visit for spine and TBLH BMD as follows:

- Baseline value
- Value at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window (if specified)
- Percentage change from baseline to each postbaseline analysis window (if specified)

In addition, descriptive statistics will be provided by cohort (and group, where applicable) and overall and by visit for the spine and TBLH BMD Z-scores (standard Z-score and height-age Z-score) as follows:

- Baseline value
- Value at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

Shift tables of clinical BMD status at baseline versus postbaseline visits will be presented for both spine and TBLH BMD. Clinical BMD status will be classified into two categories using BMD Z-scores (standard Z-score and height-age Z-score): Z-scores > -2 versus Z-scores ≤ -2 {Gordon 2008}. The shift will be from > -2 to ≤ -2.

The number and percentage of participants with at least 4% decline in BMD from baseline to each postbaseline visit will be summarized by cohort (and group, where applicable) and overall and by visit for both spine and TBLH BMD.

By-participant listings of BMD, Z-scores (standard Z-score and height-age Z-score) will be provided for spine and TBLH BMD separately.

A by-participant listing will provide participants with at least 4% decline in BMD from baseline to any postbaseline visit in either body site (ie, spine or TBLH). The BMD values, standard Z-scores, height-age Z-scores, height, and body weight will be presented.

By-participant listings of participants with spine and/or TBLH BMD Z-score that shifts from > -2 at baseline to ≤ -2 at any postbaseline visit will also be provided, from standard Z-scores and height-age Z-scores, separately.

7.2.6.2. Bone Safety Tests

Serum bone safety tests include: BsAP, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D.

Descriptive statistics will be provided by cohort (and group, where applicable) and overall and by visit for bone tests above as follows:

- Baseline value
- Value at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window (if specified)
- Percentage change from baseline to each postbaseline analysis window (if specified)

A by-participant listing will be provided for bone safety test results above, as well as N-telopeptide and N-telopeptide/creatinine from urine chemistry tests.

7.3. Tanner Stage Assessment

Tanner Stages will be used to evaluate the onset and progression of pubertal changes for children who are 6 years or older. Females will be rated for pubic hair growth and breast development, and males will be rated for pubic hair growth and genitalia development. The shift in Tanner Stages (breasts or pubic hair for female; genitalia or pubic hair for male) from baseline at all postbaseline visits will be summarized by sex, by cohort (and group, where applicable) and overall using frequency count and percentage. The maximum Tanner Stage will also be presented.

Tanner Stage results at Day 1 and during the study, if available, will be listed.

7.4. Acceptability and Palatability Assessment

Acceptability assessments will be summarized using frequency count and percentage by cohort (and group, where applicable) and overall. Palatability assessments will be summarized using frequency count and percentage by cohort (and group, where applicable) and overall, by visit.

A by-participant listing will also be provided for acceptability and palatability details.

7.5. Body Weight, Height, and Vital Signs

An age- and sex-specific Z-score will be derived for each body weight, height, and BMI measurement according to the downloadable SAS program available on the Centers for Disease Control and Prevention (CDC) website using the year 2000 growth charts. The methods and SAS program published on the following CDC websites will be applied to calculate the Z-score:

- http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/index.htm
- http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Descriptive statistics will be provided by cohort (and group, where applicable) and overall for body weight, body weight Z-score, body height, body height Z-score, BMI and BMI Z-score as follows:

- Baseline value
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

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

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

A by-participant listing of body weight, body weight Z-score, body height, body height Z-score, BMI, BMI Z-score, and BSA will be provided.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order.

7.6. 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.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug continued to be taken after the first dosing date, or which are started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last 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 or a start date after the last 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) after the study drug stop date will be excluded from 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.

7.6.1. Nonstudy-Drug Antiretroviral Medications

Nonstudy-drug medications are defined as any ARV medications other than study drug that are taken prior to, during or after the study (if collected).

Nonstudy-drug ARV medication with an end date on or 1 day before the first dose date of study drug will be considered as nonstudy-drug ARV medication received prior to the first dose date of study drug (or preswitch ARV used).

Nonstudy-drug ARV medication received prior to the first dose date of study drug will be summarized by ARV drug class and generic name for participants in the Safety Analysis Set. Multiple drug use (by drug class or generic name) will be counted only once per participant. Drug classes will be presented alphabetically and generic names within each drug class will be presented in descending order of the total frequency. No inferential statistics will be provided.

All nonstudy-drug ARV medications will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.6.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications are defined as non-ARV medications other than study drug taken while a participant receiving the study drug.

All concomitant non-ARV medications will be summarized by cohort (and group, where applicable) and overall, by preferred name. Multiple drug use (by preferred name) will be counted only once per participant. The summary will be sorted by decreasing total frequency. For drugs with the same frequency, sorting will be done alphabetically.

A by-participant listing will also be provided and sorted by participant ID number and administration date in chronological order.

7.7. Electrocardiogram Results

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

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by cohort (and group, where applicable) and overall using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

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

7.8. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number.

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

7.9. 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

Both intensive and sparse PK were collected for all participants throughout the study. Refer to Appendix 2 in the study protocol amendment 2 for schedule details for PK sample collection.

8.2. PK Analyses Related to Intensive/Sparse PK Sampling

A by-participant listing will list the available PBMC PK samples for TFV-DP concentrations and the associated results. All other analyses related to IPK and sparse PK have been completed in Interim Analysis 2. Please refer to the SAP for Interim Analysis 2 for details.

8.2.1. PK/PD Analyses

PK/PD relationships are not applicable for the study.

8.3. Changes From Protocol-Specified PK Analyses

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

9. REFERENCES

Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, et al. Dual Energy X-ray Absorptiometry Interpretation and Reporting in Children and Adolescents: The 2007 ISCD Pediatric Official Positions. J Clin Densitom 2008;11 (1):43-58.

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® Version 7.0. (Statistical Solutions, Cork, Ireland.)

11. SAP REVISION

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

12. APPENDICES

12.1. Schedule of Assessments

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								Post Week 48[b]		30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48	Every 12 Wks	Every 24 Wks		
Informed Consent/Assent	X													
Medical History[g]	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X	X
Complete Physical Exam	X	X						X		X		X[h]		X
Symptom-Directed Physical Exam[i]			X	X	X	X	X		X		X		X	
12-Lead ECG (performed supine)	X											X[j]		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X	X
Weight and Height/Length	X	X	X	X	X	X	X	X	X	X	X		X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X		X	X
Urine Chemistry		X		X	X	X	X	X		X	X			X
Selected Renal Safety Tests[k]		X		X	X	X	X	X		X	X			X[l]
CCI														
Serum Pregnancy Test[m]	X													
Urine Pregnancy Test[n]		X	X	X	X	X	X	X	X	X	X		X	X
Chemistry Profile	X	X	X	X	X	X	X	X	X	X	X		X	X
Metabolic Assessments		X						X		X		X		

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								Post Week 48[b]		30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48	Every 12 Wks	Every 24 Wks		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X		X	X
Hematology Profile	X	X	X	X	X	X	X	X	X	X	X		X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X		X	X
CD4 Cell Count	X	X	X	X	X	X	X	X	X	X	X		X	X
CCI														
Whole Blood Sample Storage		X												
Serum Storage Sample													X	X
HCV Serology[p]	X													
HBV Serology	X													
Enrollment[q]		X												
Cohort 1 Dispense Diary Cards[r]			X											
Cohorts 2, 3, & 4 Dispense Diary Cards[r]			X	X										
Single Random PK Sample[s]			X					X						
Cohorts 1 and 2 Fasted Prior to Visit		X		X	X	X	X	X		X		X		
Cohort 1 IPK Sampling[t]				X										
Cohort 2 Part A IPK Sampling[t]				X[t]	X[t]									
Cohort 1 Palatability and Acceptability Assessment[u]				X							X[u]	X[u]		
Cohort 2 Part A Palatability and														

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								Post Week 48[b]		30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48	Every 12 Wks	Every 24 Wks		
Acceptability Assessment				X	X									
Single Observed Dosing PK Sample[v]					X		X							
Trough PK Sample[s,w]						X								
PBMC[s,x]						X								
DXA Scan (spine & total body)		X						X		X		X	X[y]	X[y]
Cohort 1 Serum Bone Safety Tests[z]		X			X		X	X		X		X		X[aa]
Cohorts 2, 3, and 4 Serum Bone Safety Tests[z]		X				X	X	X		X		X		X[aa]
Tanner Stage Assessment[bb]		X						X		X	X			
In-Clinic Dosing				X	X	X	X							
Study Drug Dispensation		X			X	X	X	X	X	X	X[cc]			
Study Drug Accountability			X	X	X	X	X	X	X	X	X			X

a All study visits are to be scheduled relative to when the Baseline/Day 1 visit was completed. All study visits through Week 8 are to be completed within ± 2 days of the protocol-specified visit date. Visits between Week 12 through Week 48 are to be completed within ± 4 days of the protocol-specified visit date, unless otherwise specified.
b Post Week 48 study visits are to be completed every 12 weeks (± 10 days) unless otherwise specified.
c All screening evaluations are to be completed within 35 days prior to Baseline/Day 1 Visit.
d Participants will be dispensed study drug on the Baseline/Day 1 Visit. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit. F/TAF will be provided by the Sponsor unless prohibited by local regulations or upon request by the participant due to insurance restrictions.
e 30 Day Follow-Up only required for those participants who do not wish to continue to participate after Week 48 or those participants who permanently discontinue study drug and do not continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation (ESDD) Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Participants will be asked to continue attending the scheduled study visits through Week 48 even if the participant discontinues study drug.
g Medical history should include a history of HIV-1 disease-related events, ongoing medications within 30 days of Screening, and all information available on historical genotypes.
h Complete physical examination every 48 weeks post 48 weeks (urogenital/anorectal exams will be performed at the discretion of the Investigator).

i Symptom-directed physical examination, as needed.
j 12-lead ECG performed supine every 48 weeks post week 48.
k Renal safety tests assessments will be collected fasted for Cohorts 1 and 2. If the participant has not fasted prior to the visit the participant must return within 72 hours in a fasted state to collect urine for renal safety tests.
l Required for ESDD visit if last test was > 12 weeks from ESDD visit.
m Females of childbearing potential in Cohorts 1 and 2 only. Performed at screening and anytime during the study to confirm a positive urine pregnancy test.
n Females of childbearing potential in Cohorts 1 and 2 only. Positive urine pregnancy tests anytime during the study will be confirmed with a serum test.
[redacted]
p If the antibody test result is positive, HCV RNA test will be performed to confirm HCV viremia.
q Assignment of the participant's enrollment number may occur up to 7 days prior to the Baseline/Day 1 visit.
r Diary Cards will be dispensed at Week 1 for all participants in Cohort 1 to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit at the Week 2 visit. Diary Cards will be dispensed at Week 1 or Week 2 for all participants in Part A of Cohorts 2, 3, and 4 to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit that is to occur during the Week 2 or 4 visit, or within 7 after the completion of the Week 2 or Week 4 visit. Diary Cards are to be collected and reviewed for protocol compliance prior to in-clinic dosing and IPK sampling. If the participant has already dosed or is not fasted prior to the IPK evaluation visit refer IPK instructions in the study protocol amendment 2 Section 6.3 for details on how to proceed.
s Participants are allowed to take study drug at approximately the same time each day however at the time of the single random PK, trough PK, or PBMC sampling they are required to report the time of the last dose.
t IPK will occur during the Week 2 visit for participants in Cohort 1 and at either the Week 2 or Week 4 visit, or within 7 days after the completion of Week 2 or Week 4 visits, for participants in Cohort 2 Part A. For the purpose of scheduling the IPK visit, a +7 day window may be used. Participant dosing diary cards are to be collected and reviewed prior to in-clinic dosing and IPK sampling.
u For Cohort 1, palatability will be assessed 30 - 60 minutes after study drug dosing for all participants undergoing IPK sampling at Week 2. Acceptability will be assessed 30 - 60 minutes after study drug dosing for active participants at the next study visit immediately following approval of this protocol at the site.
v A single observed dosing PK sample will be collected at Weeks 4 and 12 at any time between 15 min to 4 hours post observed in-clinic dose. For participants in Cohort 2 Part A, a single observed dosing PK sample does not need to be collected at Week 4 if IPK is collected at the Week 4 visit.
w For participants in all Cohorts a trough PK sample will be collected during the Week 8 visit at 0 hours (pre-dose, ≤ 30 minutes prior to dosing) will be collected.
x For participants in Cohorts 1 and 2, PBMC collection will be performed at the Week 8 visit only at study sites that can perform PBMC processing. All PBMC blood samples will be collected at 0 hours (≤ 30 minutes pre-dose).
y DXA scan to be performed at the 30 Day Follow-up visit or the ESDD visit if the last scan was acquired > 12 weeks from the date of the ESDD Visit. DXA scan can occur up to 10 days after the ESDD visit date.
z If the participant has not fasted prior to the blood draw for serum bone safety tests visit may continue however the participant must return within 72 hours after completion of the visit in a fasted state to draw blood for serum bone safety tests.
aa Serum bone safety test is required at ESDD visit if last test was > 12 weeks from ESDD visit.
bb Tanner assessments will be performed at Baseline/Day1, Weeks 24 and 48 and every 12 post week 48, or until participant reaches Tanner Stage 5
cc Drug dispensation at Week 48 is only for participants that are to continue in the study post Week 48.

12.2. Data Collection of COVID-19 Data

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

12.2.1. Data Collection

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

12.2.2. Determination of Missed and Virtual Visits

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

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

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

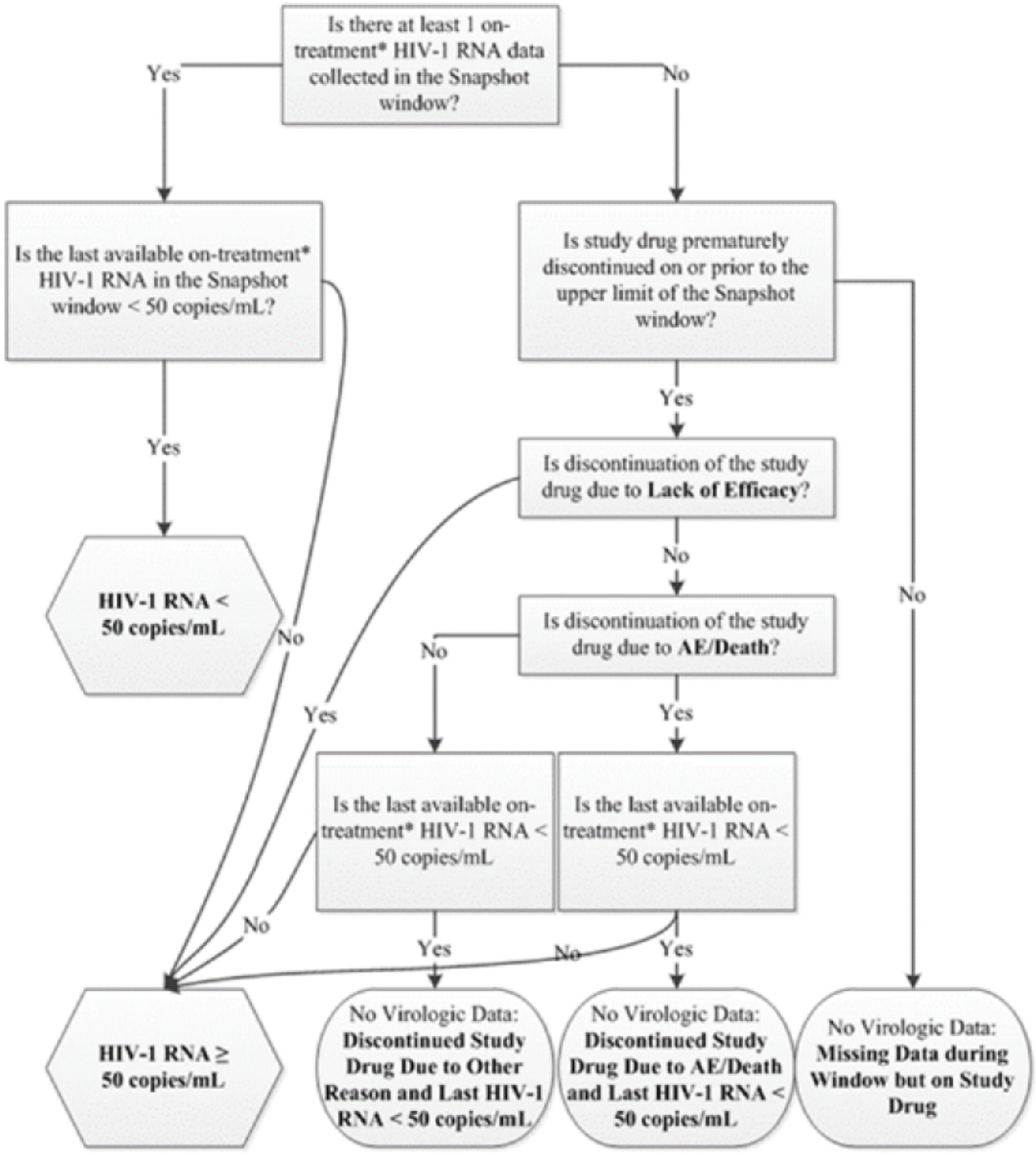
Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY

Search Terms for "COVID-19"	Search Terms for "Virtual"
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

12.3. US FDA-Defined Snapshot Algorithm

The flowchart of the US FDA-defined snapshot algorithm 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} is provided in Figure 12-1.

Figure 12-1. Flowchart of US FDA-Defined Snapshot Algorithm



* On-treatment data include all data collected up to 1 day after the last dose of study drug for participants who prematurely discontinue or complete study drug.

12.4. Programming Specification

General Conventions

1) AGE calculated as follows:

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

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

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

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

   e) If the DOB and Day 1 have the month in common and the birthday is later in the month than the date of Study Day 1, then subtract one from the AGE result above.

   For participants enrolled and never dosed with study drug, age will be calculated from the date of enrollment.

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

2) Years since participant diagnosed with HIV

   First Dose Year – Year Participant Diagnosed with HIV (if HIV was present at birth, years since participant was diagnosed will be equal to age of participant).

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

4) Screen failure participants are those participants who were screened and answered "No" for any inclusion criterion or "Yes" for any exclusion criterion regardless of which version of protocol the participant was consented to. In addition, for participants who "Met All Eligibility Criteria" ie, those who were screened but not enrolled, these are participants who answered "No" to "Was the participant enrolled" in the Enrollment eCRF.

5) Participants in the All Enrolled Analysis Set are defined as participants enrolled in the study. IXRSRAND is the source to determine whether a participant is enrolled (ie, participant with nonmissing ENRDTN in the IXRSRAND dataset), and confirmed by the ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

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

7) BMI and BSA

BMI and BSA will be calculated only at baseline as follows:

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

b) BSA (m^2) = SQRT([Height(cm) x Weight(kg)]/ 3600)

BMI and BSA are derived only at visits where both weight and height are collected. Further, if height is at screening and weight is at Day 1 and screening, the derivations would be based on the same visit (in this case screening)

Baseline is defined as the last value on or prior to Study 1 for all assessments, unless otherwise specified. Examples below:

a) If height is collected at both screening and Day 1, then Day 1 values would be used.

b) If height is collected at screening only then screening would be used.

8) "Not Permitted", "Unknown", or missing categories will be excluded for percentage calculation; except for mode of infection (HIV Risk Factors), where "Unknown" will be included for percentage calculation, since a participant may fit more than 1 HIV risk factor, and therefore percentage may add to more than 100%.

9) Last Dose Date and Last Study Date

a) Last dose date (ie, TRTEDTC or TRTEDT) in ADSL was defined in Section 3.8.1.

For participants with a partial last dosing date (ie, month and year of last dose are known), the latest of the dispensing dates of study drug bottles, study drug start dates and end dates, and the imputed last dose date [day imputed as 15] will be used as the final imputed last dose date. However, if dispensing date's month is after last dose date's month, a data query is needed.

b) Last study date is the latest of the study drug start and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date for participants who prematurely discontinued study or who completed the study according to the Study Completion eCRF. If study drug start or end date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

10) For HIV-1 RNA M = F,

M = F when

a) The participant has a visit after the missing value.

b) The participant is missing HIV-1 RNA because he/she has already discontinued the study drug.

c) The participant came for a laboratory visit for that visit, but the HIV-1 RNA value is missing (eg, sample issue).

Missing is excluded from the denominator when

d) This participant has neither baseline nor postbaseline laboratory data.

11) TEAE

Events with Missing Start Day and/or Month

An AE is TE if the following 3 criteria are met:

1. The month and year (or year) of start date is the same as or after the month and year (or year) of the first dose of study drug, and

2. The month and year (or year) of the start date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

3. End date is as follows:

   a. The (complete) end date is on or after the first dose date, or

   b. The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

   c. End date is completely missing

Events with Completely Missing Start Date

An AE with a completely missing start date is defined as TEAE if end date meets any of the criteria specified in 3) above.

12) Graded Laboratory Abnormalities Summary

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

Battery	Laboratory Test Label Used in l-labtox Listing	Toxicity Direction	Laboratory 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)
	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)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
Urinalysis	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative)

13) For figures, if at a visit where n (sample size) ≤ 5, data will not be displayed at the visit in figure (except the Kaplan-Meier figure), but all data will be included in the corresponding table summary.

14) LDL: Conversions between second and third generations

LDL was analyzed by 2 different assays in the study: second generation (including RCT2394, RCT2312, and RCT2811) and third generation (RCT3870). Samples collected at earlier visits were analyzed using LDL second generation assay. Samples collected at later visits were analyzed using LDL third generation assay. The conversion formulas are as follow:

a) second generation (mmol/L) = (third generation − 0.0626)/0.882

b) third generation (mmol/L) = (0.882 x second generation) + 0.0626

For this analysis, since LDL samples were analyzed by second generation assay at Baseline, only conversion from third generation to second generation was requested.

For the analysis of change from baseline in fasting direct LDL: the sample analyzed by LDL third generation assay will be converted to second generation as a new record with test codes of LIP.LDL.00.02 in raw data. During ADaM stage, a derived parameter code (FLDL2) for "Fasting LDL Cholesterol 2ND GEN Combined" will be generated to pool the records from both original (including test codes RCT2394, RCT2312, and RCT2811) and converted (LIP.LDL.00.02) second generation results to calculate the change from baseline in fasting direct LDL.

For the analysis of toxicity grade for fasting direct LDL: toxicity grade will be based on the Gilead grading results (ie, toxgrg) from original values before conversion. In other words, during ADaM stage, a derived parameter code (FLDLTOX) for "Fasting LDL Cholesterol for Toxicity" will be generated to pool the records from second generation (including RCT2394, RCT2312, and RCT2811) and third generation (ie, RCT3870) to derive treatment-emergent toxicity grades, maximum postbaseline toxicity grades, etc.

15) Previously, for the lab test of "UR.N-TELO/CREAT RATIO", it came from LBTESTCD = IMT1619, which had the unit value of "nmol BCE/mmol Creat". Due to a LabCorp assay update, a new test ID has been used with a LBTESTCD = IMT3019, which has a new unit value of ""nmol BCE/mmol C". The discrepancy of unit under the same test name will cause an P21 Error "(SD0007 – Inconsistent value for Standard Units)". LabCorp was not able to update the unit name to match the previous unit name, but confirmed both tests measured the same parameter and results were interchangeable. Thus, the unit was updated in SDTM level, for COVLAB.LBTESTCD = IMT3019 the unit was updated as "nmol BCE/mmol Creat" to match the previous unit value.

16) In COVLAB raw data, LBTESTCD that are LAT1939 and ERT786 are both immunoassay performed on Serum, testing the same parameter "carboxyterminal telopeptide type 1 collagen", the test name was given differently depending on the region that is using the test (ie, Americas versus Europe). LAT1939 was updated to ERT786 in October 2018 as LAT1939 test was discontinued in LabCorp (ERT786 is performed by an external laboratory).

17) In COVLAB, the alert flag (ALRTFL) for lab test "Beta 2 Microglobulin" (LBTESTCD = SCT3094) is age dependent. Participants from 0Y to <18Y has no reference range, and participants from >=18Y to < 150 Y with results > 0.3mg/L is flagged as "H".

18) The following columns headers will be used for tables:

a) Cohort 1 (12 to < 18 years and ≥ 35 kg)

b) Cohort 2 Group 1 (6 to < 12 years and ≥ 25 kg)

c) Cohort 2 Group 2 (2 to < 12 years and 17 to < 25 kg)

d) Total

19) For rescreened participants, the later records will be used.

20) For DXA analysis,

a) Variable CORCCBMD when Region = "SpineTotalAdequate" for spine and Region = "BodyTotalNoHead" for TBLH BMD analysis.

b) Variable CORCCZCR when Region = "SpineTotalAdequate" for spine and Region = "BodyTotalNoHead" for TBLH standard Z-score analysis.

c) Variable CORCCHAZ when Region = "SpineTotalAdequate" for spine and Region = "BodyTotalNoHead" for TBLH height-age Z-score analysis.

For c), corrected cross calibrated height-age Z-score will only be available when reference is available for extrapolation.

21) For HBV surface antigen/antibody, and HCV antibody, only display missing category when applicable in the data.

22) For PBMC reporting, from source PK data there were two different types of concentrations: VOLCONC and CONCC. For reporting, only report the intracellular concentration, which is CONCC (in ng/million cells). Intracellular concentration should be reported in both ng/million cells and fmol/million cells. The conversion between the two is: fmol/million cells = ng/million cells × 1000000/447.17.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	19-Feb-2025 23:01:01
PPD	Clinical Pharmacology eSigned	21-Feb-2025 05:15:21
PPD	Global Development Lead (GDL) eSigned	22-Feb-2025 00:13:23