STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) STR; Genvoya®
Study Number:	GS-US-292-0106
Protocol Version (Date):	Amendment 7 (01 June 2021); Amendment 7.1 (25 June 2021)
Analysis Type:	Final Analysis
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CCG	eCRF completion guidelines
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COBI	cobicistat, Tybost®
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CTX	C-telopeptide
CV	coefficient of variation
CSR	clinical study report
DMC	data monitoring committee
DOB	date of birth
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EVG	elvitegravir, Vitekta®
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTC	emtricitabine, Emtriva®
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
ID	identification
IPK	intensively sampled pharmacokinetic(s)

LD	low dose
LDL	low-density lipoprotein
LLT	lower-level term
LOQ	limit of quantitation
M=E	missing = excluded
M=F	missing = failure
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search term
n	number of participants
NLP	natural language processing
P1NP	procollagen type I N-terminal propeptide
PK	pharmacokinetic(s)
PBMC	peripheral blood mononuclear cells
PopPK	population pharmacokinetic(s)
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
RBP	retinol-binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	standardized MedDRA query
SOC	system organ class
STR	single tablet regimen
TAF	tenofovir alafenamide, Vemlidy®
TBLH	total body less head
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TELA	treatment-emergent laboratory abnormality
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir diphosphate
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
AUC	area under the concentration versus time curve
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
CL	clearance
CL_{ss}/F	apparent oral clearance at steady-state
C_{tau}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z	volume of distribution
V_z/F	apparent 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-292-0106. This SAP is based on study protocol amendment 7 dated 01 June 2021, study protocol amendment 7.1 dated 25 June 2021, 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

1.1.1. Cohort 1

The primary objectives for Cohort 1 are:

- Part A
  - To evaluate the steady state pharmacokinetics (PK) for elvitegravir (EVG) and tenofovir alafenamide (TAF) and confirm the dose of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected, antiretroviral (ARV) treatment-naive adolescents
- Part B
  - To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 24 in HIV-1 infected, ARV treatment-naive adolescents

The secondary objectives for Cohort 1 are:

- To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents
- To evaluate the antiviral activity of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents

1.1.2. Cohort 2

The primary objectives for Cohort 2 are:

- Part A
  - To evaluate the PK of EVG and TAF in virologically suppressed HIV-1 infected children 6 to < 12 years of age, weighing ≥ 25 kg, administered E/C/F/TAF STR

- Part B

  — To evaluate the safety and tolerability of E/C/F/TAF STR through Week 24 in virologically suppressed HIV-1 infected children 6 to < 12 years of age

The secondary objectives for Cohort 2 are:

- To evaluate the antiviral activity of switching to E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age weighing ≥ 25 kg
- To evaluate the safety and tolerability of E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age, weighing ≥ 25 kg

1.1.3. Cohort 3

The primary objectives for Cohort 3 are:

- To evaluate the PK of EVG and TAF and confirm the dose of the STR in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg administered E/C/F/TAF low dose (LD) (90/90/120/6 mg) STR
- To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 24 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg

The secondary objectives for Cohort 3 are:

- To evaluate the antiviral activity of switching to E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg
- To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg

1.1.4. All Cohorts

CCI [redacted]

[redacted]

1.2. Study Design

This is a Phase 2/3 open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF STR in HIV-1 infected ARV treatment-naive adolescents and virologically suppressed children.

Antiretroviral treatment-naive, HIV-1 infected adolescents (12 to < 18 years of age) of either sex with plasma HIV-1 RNA levels ≥ 1,000 copies/mL as well as virologically suppressed, HIV-1 infected children (≥ 2 to < 12 years of age and screening weight ≥ 14 kg) of either sex with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening on a stable ARV regimen, with no documented history of resistance to any component of E/C/F/TAF STR were eligible for entry into the study (refer to study protocol amendment 7 for complete inclusion and exclusion criteria).

A total of 50 adolescents (12 to < 18 years of age), and up to 75 children (2 to < 12 years of age and screening weight ≥ 14 kg) of either sex was planned to be enrolled.

Table 1-1. Study Treatments

Cohort	Age Range	Weight Range at Screening	Dose
1	12 to < 18 years of age	≥ 35 kg	EVG 150-mg/COBI 150-mg/FTC 200-mg/TAF 10-mg STR administered orally once daily with food
2	6 to < 12 years of age	≥ 25 kg	EVG 150-mg/COBI 150-mg/FTC 200-mg/TAF 10-mg STR administered orally once daily with food
3	≥ 2 years of age	≥ 14 to < 25 kg	EVG 90-mg/COBI 90-mg/FTC 120-mg/TAF 6-mg LD STR administered orally once daily with food

COBI = cobicistat, EVG = elvitegravir, FTC = emtricitabine, LD = low dose, STR = single tablet regimen, TAF = tenofovir alafenamide, TFV = tenofovir.

No randomization was used in this study due to the study design.

The study consists of 2 phases: a 48-week main phase, followed by an extension phase. After completing 48 weeks of treatment, all participants were given the option to participate in an extension phase of the study where Gilead provided E/C/F/TAF STR until: a) the relevant E/C/F/TAF STR formulation was available for use, other than through the study, in the country in which the participant was enrolled, or b) Gilead Sciences elected to terminate development of E/C/F/TAF STR in the applicable country. Participants who were no longer taking study drug at Week 48 were not eligible to participate in the study extension. Participants returned for study visits every 12 weeks in the extension phase. After Week 240 in Cohorts 1 and 2 and after Week 96 in Cohort 3, participants returned for study visits every 24 weeks for the duration of the extension phase.

At Screening, Baseline/Day 1, and all subsequent study visits laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, vital signs, and complete or symptom-directed physical examinations and estimated glomerular filtration rate (eGFR) using the Schwartz formula were performed.

Adverse events (AEs) and concomitant medications were assessed at each visit.

Participants enrolled in Part A participated in an intensively sampled PK (IPK) evaluation at Weeks 2 (Cohort 3, all participants) or 4 (Cohorts 1 and 2). Participant diary cards were provided to all Part A participants to record administration of study drugs prior to the IPK visit.

For participants in Cohorts 1 and 2, a trough PK sample (20 to 24 hours post-dose) was collected at Weeks 1, 2, and 24. For Cohort 1, a trough PK sample was also collected at Week 48. For participants in Cohort 3, a trough sample was collected at Weeks 4 and 24.

For participants in Cohort 1, a timed random PK sample was collected between 0.25 to 4 hours post-dose at Weeks 4 (Cohort 1 Part B participants only) and 12 (all Cohort 1). A random PK sample was collected at Weeks 8, 16, 32, and 40. For participants in Cohort 2, a timed random PK sample was collected between 0.25 to 4 hours post-dose at Week 12 and a random single PK sample was collected at Weeks 8 and 16. For participants in Cohort 3, a timed single PK sample was collected between 0.25 to 4 hours post-dose at Weeks 8, 12, and 16.

Tanner stage was assessed for participants ≥ 6 years of age at Baseline, Weeks 24 and 48 or until participants reached Tanner Stage 5, after which point Tanner assessments were no longer performed. For all cohorts, dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body were performed at Baseline, Weeks 24 and 48 to measure spine bone mineral density (BMD) and total body less head (TBLH) BMD.

Additional details regarding study assessments can be found in Section 12.1.

1.3. Sample Size and Power

1.3.1. Cohorts 1 and 2

A minimum of 18 Part A participants from each cohort received E/C/F/TAF STR in this study. Pharmacokinetic data from these participants will have 92% power to conclude exposure equivalence of TAF AUC_{last} in adolescents and children, respectively versus. 51 HIV-1 infected and HIV negative adults (Studies GS-US-292-0102 and GS-US-292-0103 combined) using two one-sided tests with each performed at an alpha level of 0.05. In this power analysis, it is assumed that the expected geometric mean ratios of TAF AUC_{last} between adolescent group and adult group are equal to 1, and the inter-participant standard deviation (SD) (natural log scale) of TAF AUC_{last} is 0.37 ng•hr/mL, and the equivalency boundary is 70% to 143%.

A minimum of 18 Part A participants from each cohort will also provide > 99% power to target a 95% confidence interval (CI) within 60% and 140% of the geometric mean estimate of apparent CL and V_z of TAF respectively, assuming a coefficient of variation (CV) of 38% for CL and 42% for V_z (Studies GS-US-292-0102 and GS-US-292-0103 combined).

For each cohort, a total of 50 participants (participants from Part A and participants from Part B combined) is planned to study the safety of the E/C/F/TAF STR. With this sample size, the present study will have 92% chance to observe at least 1 SAE, assuming the SAE incidence rate is 5% (observed in GS-US-292-0102).

After study protocol amendment 2 was finalized, the adult data included in the Genvoya label became available and will be used as historical control for comparison for Cohort 2 (ie, IPK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK [PopPK] data from 539 HIV-1 infected adults in Studies GS-US-292-0104 and GS-US-292-0111 combined for TAF AUC_{last}). Given the actual number of enrollments in Cohort 2 Part A is 23, a total of 23 participants will provide 90% power for EVG AUC_{tau} and 88% power for TAF AUC_{last} to conclude exposure equivalence between adults and children. In this power analysis, it is assumed that the expected geometric mean ratios are equal to 1, the interparticipant SD (natural log scale) of EVG AUC_{tau} and TAF AUC_{last} is 0.34 ng•hr/mL and 0.52 ng•hr/mL, respectively, 2 one-sided statistical tests are done at an alpha level of 0.05, and the equivalency boundary is 70% to 143%.

A total of 23 participants will also provide > 86% power to target a 95% CI within 60% and 140% of the geometric mean estimate of CL and Vz of TAF respectively, assuming a CV of 53% for CL and 76% for V_z (based on PopPK data from Studies GS-US-292-0104 and GS-US-292-0111 combined).

1.3.2. Cohort 3

Twenty-five evaluable participants compared to historical adult data will provide 90% power for each of EVG AUC_{tau} and TAF AUC_{tau} to conclude exposure equivalence between children and adults. In this power analysis, it is assumed that the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level

of 0.05, and the inter-participant SD (natural log scale) of EVG AUC_{tau} and TAF AUC_{tau} are 0.34 ng•hr/mL and 0.52 ng•hr/mL respectively. For historical adult data, IPK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and PopPK data from Studies GS-US-292-0104 and GS-US-292-0111 combined for TAF AUC_{tau} was used.

Twenty-five evaluable participants will also provide > 99% power to target a 95% CI within 60% and 140% of the geometric mean estimate of apparent CL and V_z of TAF respectively, assuming the SD in natural log scale is 0.51 for CL and 0.54 for V_z (based on PopPK data from Studies GS-US-292-0104 and GS-US-292-0111 combined).

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

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Interim Analysis 1

This analysis included data collected from Cohort 1 Part A and B only. It was conducted after 23 participants enrolled by 11 February 2014 from both Part A and Part B of Cohort 1 completed their Week 24 visit or prematurely discontinued study drug.

The SAP for Interim Analysis 1 describes the analysis plan for Interim Analysis 1.

2.1.2. Interim Analysis 2

This analysis included data collected from Cohort 1 Part A and B only. It was conducted after all participants in Cohort 1 Part A and B completed their Week 48 visit or prematurely discontinued study drug.

The SAP for Interim Analysis 2 describes the analysis plan for Interim Analysis 2.

2.1.3. Interim Analysis 3

This analysis included data collected from Cohort 2 Part A. It was conducted after all participants in Cohort 2 Part A completed their Week 24 visit or prematurely discontinued study drug.

The SAP for Cohort 2 Part A Week 24 Analysis describes the analysis plan for Interim Analysis 3.

2.1.4. Interim Analysis 4

This analysis included data collected from Cohorts 1 and 2 only. It was conducted after all participants in Cohorts 1 and 2 had completed their Week 96 visit (for Cohort 1) or Week 48 visit (for Cohort 2), or prematurely discontinued study drug.

The SAP for Interim Analysis 4 describes the analysis plan for Interim Analysis 4.

2.1.5. Interim Analysis 5

This analysis included data collected from Cohort 3 only. It was conducted after all Cohort 3 participants had completed their Week 48 visit or prematurely discontinued study drug.

The SAP for Interim Analysis 6 describes the analysis plan for Interim Analysis 5. It was originally planned to conduct Interim Analysis 5 after all Cohort 3 participants had completed their Week 24 visit or prematurely discontinued study drug; a SAP was approved for that analysis and is referred to as the SAP for Interim Analysis 5. However, the study team later

decided that the analysis detailed in the SAP for Interim Analysis 5 was not needed and instead the analysis would be conducted after all Cohort 3 participants had completed their Week 48 visit or prematurely discontinued study drug. A separate SAP (SAP for Interim Analysis 6) was then written and approved.

2.1.6. Data Monitoring Committee Analyses

An external independent multidisciplinary Data Monitoring Committee (DMC) reviewed the progress of the study and performed interim reviews of the safety and efficacy data in order to protect participant welfare and preserve study integrity. To ensure the best interests of the participants, the DMC could make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warranted the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The first DMC analysis was conducted after the first 18 participants enrolled in Cohort 1 Part A completed an IPK evaluation at Week 4. The DMC convened on 27 February 2014, reviewed the available data and determined that the study could continue according to the protocol without modification. It was also agreed that Cohort 1 Part B could open for enrolment and that the review of the Week 12 data could include only Part A data.

The second DMC analysis was conducted after the first 18 participants enrolled in Cohort 1 Part A completed their Week 12 visit or prematurely discontinued study drug. The DMC convened on 21 October 2014, reviewed the available data and determined that the study could continue according to the protocol without modification. It was confirmed that the data presented met the specified criteria for review of Week 12 data. The DMC agreed that they would review the comparative safety data between GS-US-292-0106 and GS-US-236-0112.

The third DMC analysis was conducted after all participants enrolled in Cohort 1 either completed the Week 24 visit or prematurely discontinued study drug. The DMC convened on 10 July 2015, reviewed the available data (including cross-study comparison for renal and bone safety data of the two study drugs) and determined that the study could continue according to the protocol without modification.

The fourth DMC analysis was conducted after all participants enrolled in Cohort 2 Part A completed an IPK evaluation at Week 4. The DMC convened on 06 May 2016, reviewed the available data and determined that the study could continue according to the protocol without modification. By that date all participants in Cohort 2 Part A had already completed their Week 12 visits; therefore the DMC did not convene for a separate Week 12 DMC meeting.

After the fourth DMC analysis, it was clarified that approval of safety data for a new cohort to enroll is a pivotal point in pediatric studies in HIV-1. Thus, the review of data that allows a new cohort to enroll is best placed at a point where all participants have undergone IPK evaluation and 50% of participants have reached Week 12 or prematurely discontinued study drug. The DMC review of Week 24 safety data was removed due to this revised schedule that allows for continued study conduct without the need for additional review at this time point as this is frequently when a study's primary endpoint occurs, and the data undergoes regulatory review.

For this study, the Cohort 2 Part A Week 24 data were already submitted on 03 April 2017 to U.S. Food and Drug Administration (FDA) for review. A Week 24 safety analysis by the DMC for this study was therefore not required.

The fifth DMC was conducted after all participants enrolled in Cohort 3 completed Week 24 visits or prematurely discontinued study drug. The DMC convened on 26 October 2020, reviewed the available data and determined that the study could continue according to the protocol without modification.

The DMC's role and responsibilities and the scope of analysis were provided to the DMC in a mutually agreed upon charter, which defined the DMC membership, meeting logistics, and meeting frequency.

2.2. Final Analysis

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

2.3. Changes From Protocol-Specified Planned Analyses

The timing of the analysis of the DMC review was changed from the IPK visit to Week 24 after the fourth DMC, so that DMC members would have enough safety data for review.

A separate Week 24 analysis for Cohort 3 was not performed; it was part of Week 48 analysis for Cohort 3.

A long-term safety analysis describing safety (with a particular focus on bone and renal safety) and efficacy results was also conducted for participants in Cohorts 1 and 2 receiving the adult strength E/C/F/TAF tablet through median (Q1, Q3) exposures of 312.1 (132.7, 336.0) and 168.1 (156.4, 251.9) weeks, respectively. The statistical methodology outlined in the SAP for Interim Analysis 4 was applied.

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 and sorted by cohort, 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 to which participants were enrolled will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

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

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

A listing of participants excluded from any analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set will include all participants who received a study participant identification number in the study after screening.

3.1.2. Full Analysis Set

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

Note: For FAS analysis, all efficacy data, including data collected after the last dose date of study drug, will be included, unless specified otherwise.

3.1.3. Safety Analysis Set

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

Note: All data collected from the first dose date up to 30 days after participants permanently discontinue their study drug will be included in the safety summaries**.**

3.1.4. DXA Analysis Set

3.1.4.1. Spine DXA Analysis Set

The Spine DXA Analysis Set will include all enrolled participants in the study who took at least 1 dose of study drug and have a nonmissing baseline as well as at least 1 postbaseline spine BMD value.

3.1.4.2. Total Body Less Head DXA Analysis Set

The TBLH DXA Analysis Set will include all enrolled participants in the study who took at least 1 dose of study drug and have a nonmissing baseline as well as at least 1 postbaseline TBLH BMD value.

3.1.5. IPK Analysis Set

Note: All required IPK analyses have already been reported and will not be repeated for the Final Analysis CSR.

The IPK Analysis Set included all enrolled participants in the study who took at least 1 dose of study drug and had any nonmissing key PK parameter (AUC_{tau}, AUC_{last}, C_{max}) from Week 2 IPK data for the respective analyte. This was the primary analysis set for IPK analyses.

The IPK Analysis Set was defined separately for each of the 5 analytes (EVG, COBI, FTC, TAF, and TFV).

3.1.6. PK Analysis Set

Note: All required PK analyses have already been reported and will not be repeated for the Final Analysis CSR.

The PK Analysis Set included all enrolled participants in the study who took at least 1 dose of study drug and had at least 1 observed single or trough concentration data for the respective analyte. This was the primary analysis set for single and trough blood concentration analyses.

The PK Analysis Set was defined separately for each of the 5 analytes (EVG, COBI, FTC, TAF, and TFV).

3.1.7. PBMC PK Analysis Set

Note: All required PBMC analyses have already been reported and will not be repeated for the Final Analysis CSR.

The PBMC PK Analysis Set included all enrolled participants in the study who took at least 1 dose of study drug for whom concentration data of TFV-DP were available. This was the primary analysis set for PK analyses of TFV-DP.

3.2. Participant Grouping

Participants enrolled in Cohort 1 (age 12 to < 18 years and weight ≥ 35 kg), Cohort 2 (age 6 to < 12 years and weight ≥ 25 kg) and Cohort 3 (age ≥ 2 years and weight 14 to < 25 kg) will be summarized separately.

As this is a single-arm, multicohort study the participants will be grouped into 1 treatment group (ie, E/C/F/TAF) per cohort and overall, for efficacy and safety analyses.

3.3. Strata and Covariates

This study is not randomized; hence it did not use a stratified randomization schedule when enrolling participants. No covariates will be included in efficacy and 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 4.2. 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 7.5.

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 $eGFR_{Schwartz}$, 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 data) that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

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

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

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

- For direct bilirubin, a value of "< 0.1" is imputed as "0.09". For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios.

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

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

Study Day 1 is the day of first dose of study drug administration.

Last Dose Date is defined as the maximum and nonmissing end date of study drug E/C/F/TAF on the study drug administration eCRF with "Study Drug Permanently Discontinued" box checked for participants a) who prematurely discontinued study drug from main phase, b) completed study drug in the main phase but did not participate in the extension phase according to study drug completion eCRF, or c) discontinued study drug during the extension phase according to the extension study drug completion eCRF.

If the date of last dose is incomplete or missing (eg, due to lost to follow-up), the last dose date will be imputed using the instruction described in Section 12.5.

Last Study Date is the maximum 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, c) discontinued study from the extension phase according to the extension study completion eCRF.

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1. The baseline DXA value is defined as 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 chemistry laboratory tests, estimated glomerular filtration rate $eGFR_{Schwartz}$, height, hematology laboratory tests, HIV-1 RNA, urinalysis laboratory tests, vital signs, and weight are provided in Table 3-1 and Table 3-2

Table 3-1. Analysis Visit Windows for Chemistry Laboratory Tests, $eGFR_{Schwartz}$, Height, Hematology Laboratory Tests, HIV-1 RNA, Urinalysis Laboratory Tests, Vital Signs, and Weight for Cohorts 1 and 2

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	9
Week 2	14	10	20
Week 4	28	21	41
Week 8	56	42	69

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 12	84	70	97
Week 16	112	98	139
Week 24	168	140	195
Week 32	224	196	251
Week 40	280	252	307
Week 48	336	308	377
Week K (K is every 12 weeks after Week 48 until Week 228)	K*7	[(K-6)*7]	[(K+6)*7]-1
…	…	…	…
Week 240	1680	1638	1763
Week L (L is every 24 weeks after Week 240)	L*7	[(L-12)*7]	[(L+12)*7]-1

After the Week 240 Visit for Cohorts 1 and 2, fasting glucose was done as part of the chemistry panel.
Parameter details for chemistry and hematology laboratory tests are provided in Section 7.2.1.
Vital signs include blood pressure, pulse, respiration rate, and temperature.

Table 3-2. Analysis Visit Windows for Chemistry Laboratory Tests, $eGFR_{Schwartz}$, Height, Hematology Laboratory Tests, HIV-1 RNA, Urinalysis Laboratory Tests, Vital Signs, and Weight for Cohort 3

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	9
Week 2	14	10	20
Week 4	28	21	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	139
Week 24	168	140	195
Week 32	224	196	251
Week 40	280	252	307
Week 48	336	308	377

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week K (every 12 weeks after Week 48 until Week 84)	K*7	[(K-6)*7]	[(K+6)*7]-1
…	…	…	…
Week 96	672	630	755
Week L (L is every 24 weeks after Week 96)	L*7	[(L-12)*7]	[(L+12)*7]-1

After the Week 96 Visit for Cohort 3, fasting glucose was done as part of the chemistry panel.
Parameter details for chemistry and hematology laboratory tests are provided in Section 7.2.1.
Vital signs include blood pressure, pulse, respiration rate, and temperature.

The analysis windows for CD4 cell counts and CD4% are provided in Table 3-3 and Table 3-4.

Table 3-3. Analysis Visit Windows for CD4 Cell Counts and CD4% for Cohorts 1 and 2

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	14	2	20
Week 4	28	21	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	139
Week 24	168	140	195
Week 32	224	196	251
Week 40	280	252	307
Week 48	336	308	377
Week K (K is every 12 weeks after Week 48 until Week 228)	K*7	[(K-6)*7]	[(K+6)*7]-1
…	…	…	…
Week 240	1680	1638	1763
Week L (L is every 24 weeks after Week 240)	L*7	[(L-12)*7]	[(L+12)*7]-1

Table 3-4. Analysis Visit Windows for CD4 Cell Counts and CD4% for Cohort 3

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	14	2	20
Week 4	28	21	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	139
Week 24	168	140	195
Week 32	224	196	251
Week 40	280	252	307
Week 48	336	308	377
Week K (every 12 weeks after Week 48 until Week 84)	K*7	[(K-6)*7]	[(K+6)*7]-1
…	…	…	…
Week 96	672	630	755
Week L (L is every 24 weeks after Week 96)	L*7	[(L-12)*7]	[(L+12)*7]-1

The analysis windows for metabolic assessments and Tanner Stage assessments are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for Metabolic Assessments and Tanner Stage Assessments

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	251
Week 48	336	252	503
Week K (K is every 48 weeks after Week 48)	K*7	[(K-24)*7]	[(K+24)*7]-1

Parameter details for metabolic assessments are provided in Section 7.2.1.
Tanner Stage assessments will be performed on participants ≥ 6 years of age and no longer be performed once a participant has been documented as Tanner Stage 5.

The analysis windows for fasting glucose assessments are provided in Table 3-6.

Table 3-6. Analysis Visit Windows for Fasting Glucose Assessments

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 8	56	2	69
Week 12	84	70	125
Week 24	168	126	251
Week 48	336	252	503
Week K (K is every 48 weeks after Week 48)	K*7	[(K-24)*7]	[(K+24)*7]-1

After the Week 240 Visit for Cohorts 1 and 2 and after the Week 96 visit for Cohort 3, fasting glucose was done as part of the chemistry panel.

The analysis windows for DXA assessments are provided in Table 3-7.

Table 3-7. Analysis Visit Windows for DXA Assessments

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	≤ 21
Week 24	168	22	251
Week 48	336	252	503
Week K (K is every 48 weeks after Week 48)	K*7	[(K-24)*7]	[(K+24)*7]-1

The analysis windows for bone safety assessments are provided in Table 3-8, Table 3-9, and Table 3-10.

Table 3-8. Analysis Visit Windows for Bone Safety Assessments for Cohort 1

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 8	56	2	69
Week 12	84	70	125
Week 24	168	126	251

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 48	336	252	419
Week K (K is every 24 weeks after Week 48)	K*7	[(K-12)*7]	[(K+12)*7]-1

Parameter details for metabolic assessments are provided in Section 7.2.1.

Table 3-9. Analysis Visit Windows for Bone Safety Assessments for Cohort 2

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	125
Week 24	168	126	251
Week 48	336	252	419
Week K (K is every 24 weeks after Week 48)	K*7	[(K-12)*7]	[(K+12)*7]-1

Parameter details for bone safety assessments are provided in Section 7.2.1.

Table 3-10. Analysis Visit Windows for Bone Safety Assessments for Cohort 3

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	125
Week 24	168	126	251
Week 48	336	252	377
Week 60	420	378	461
Week 72	504	462	545
Week 84	588	546	629
Week 96	672	630	839
Week K (K is every 48 weeks after Week 96)	K*7	[(K-24)*7]	[(K+24)*7]-1

Parameter details for bone safety assessments are provided in Section 7.2.1.
Urine bone safety markers were not collected for Cohort 3.

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 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 electrocardiogram [ECG] findings) for categorical data. The exception is for HIV-1 RNA (see below).

- For postbaseline values:

  — 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 BMD bone loss where bone loss is ≥ 4% from the previous visit or baseline, repeated measurements are taken to confirm the bone loss (bone loss repeat visit). This repeated result is, from a clinical perspective, based on a confirmed result. For repeated 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 2 measurements and others for the same participant will only have 1.

  — For other numeric observations (ie, except HIV-1 RNA, CD4 cell count, CD4%, spine BMD where bone loss repeat visit occurs), the record closest to the nominal day for that visit will be selected with the exception of viral load in which the latest record will be selected. If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — For any numeric observations except HIV-1 RNA, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

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 portion 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.

If multiple valid nonmissing categorical observations exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal).

- For postbaseline visits, the most conservative value within the window will be selected (eg, abnormal will be selected over normal).

  — The record closest to the nominal day for that visit will be selected with the exception of HIV-1 RNA for which the latest record will be selected.

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

  — If there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

3.9. Changes From Protocol-Specified Planned Analyses

The Spine BMD Analysis Set and TBLH BMD Analysis Set have been renamed Spine DXA Analysis Set and TBLH DXA Analysis Set, respectively.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant enrolled, last participant enrolled, last participant last visit for the primary endpoint (ie, Week 24), and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided by cohort for each country, investigator, 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 overall. This summary will present the number of participants screened, the number of screen failure participants, the number of participants who met all eligibility criteria but were not enrolled, the number of participants enrolled, the number of participants enrolled but never treated, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- FAS
- Completed study drug (for each study phase)
- Did not complete study drug with reasons for premature discontinuation of study drug (for each study phase)
- Completed study (for each study phase)
- Did not complete the study with reasons for premature discontinuation of study (for each study phase)

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

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

- Participant profile, including cohort, date enrolled, first dose date, last dose date and day, last visit date and day, last lab date and day, last study date and day
- Enrollment, including cohort, date informed consent signed, enrollment protocol version

- Participant disposition, including cohort, date of enrollment, first dose date, last dose date and day, study drug discontinuation, study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure and Adherence

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 date of last dose is incomplete or missing (eg, due to lost to follow-up), the last dose date will be imputed using the instruction described in Section 12.5.

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), ≥ 16 weeks (112 days), ≥ 24 weeks (168 days), ≥ 32 weeks (224 days), ≥ 40 weeks (280 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), and every 12 weeks (84 days) thereafter. Summaries will be provided by cohort and overall for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of tablets administered will be summarized using descriptive statistics.

The numbers of tablets dispensed and returned are captured on the Drug Accountability eCRF. Adherence (%) to study drug will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{\text{Total Treatment taken}}{\text{Total Treatment prescribed}}$$

$$= 100 \times \frac{\sum \text{Treatment taken at each dispensing period [1]}}{\sum \text{Treatment prescribed at each dispensing period [2]}}$$

[1] Number of tablets taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of tablets prescribed for the study drug multiplied by the duration of treatment at the dispensing period, and (b) the number of tablets taken for the study drug (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 a distinct dispensing period for a study drug is calculated as the daily number of tablets prescribed for the study drug multiplied by the duration of treatment at the 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) last returned date of study drug at a dispensing period, (b) date of premature discontinuation of the study drug, and (c) next dispensing date of the study drug, minus dispensing date of the study drug. The next tablet dispensing date is the following dispensing date 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 zero. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, then all records in that dispensing period for that study drug will be excluded from both the denominator and numerator calculation.

Adherence will be calculated for each participant 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 or using all data available for participants who have completed study drug.

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

No formal statistical testing is planned.

A by-participant listing of study drug administration and drug accountability will be provided separately by cohort and 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 and the number of participants who did not meet specific criteria by cohort 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 overall as well as deviation category for the All Enrolled Analysis Set. Additionally, the number and percentage of participants with at least 1, 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 Disaster or Public Health Emergency Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which had 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 Section 12.2 for data collection and determination of COVID-19 impacted Data.

4.4.1. Study Drug or Study Discontinuation Due to Disaster or Public Health Emergency

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

4.4.2. Protocol Deviations Due to Disaster or Public Health Emergency

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 non-important 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 overall.

A by-participant listing will be provided for participants with protocol deviations related to COVID-19.

4.4.3. Missed and Virtual Visits due to Disaster or Public Health Emergency

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by cohort and 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 Section 12.2.

4.4.4. Adverse Events Due to Disaster or Public Health Emergency

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, age group [≥ 2 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years], 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 [BSA; in m^2] and Tanner stage) will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. Tanner stage will be summarized separately for each sex (breasts, pubic hair, and maximum stage for female; genitalia, pubic hair, and maximum stage for male). 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.

Further details on Z-scores are provided in Section 7.4.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4 cell count (cells/µL)
- CD4 cell count categories (cells/µL): (a) < 200, (b) ≥ 200 to < 350, (c) ≥ 350 to < 500, (d) ≥ 500
- CD4 (%)
- HIV disease status: (a) AIDS, (b) asymptomatic, (c) symptomatic HIV infection
- Mode of infection (HIV risk factor): (a) heterosexual sex, (b) homosexual sex, (c) IV drug use, (d) transfusion, (e) vertical transmission, (f) other
- Years diagnosed with HIV
  - Calculated as: 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).
- HBV surface antigen: (a) positive, (b) negative

- HCV antibody: (a) positive, (b) negative
- eGFR calculated by the Schwartz Formula (Section 12.4)
- Proteinuria by urinalysis (dipstick): (a) Grade 0, (b) Grade 1, (c) Grade 2, (d) Grade 3

These baseline characteristics will be summarized by cohort 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.

By-participant listings of other baseline characteristics will be provided by cohort and participant ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied). Medical history will be coded using the current MedDRA dictionary.

General 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

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 analysis window at Week 24 is defined as from Study Day 140 to Study Day 195.

All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL**: This includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 24 analysis window.
- **HIV-1 RNA ≥ 50 copies/mL**: This includes participants:
  - Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window, or
  - Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and
    - Discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or
    - Discontinue study drug prior to or in the Week 24 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
    - Discontinue study drug prior to or in the Week 24 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL.

- **No Virologic Data in the Week 24 Window**: This includes participants who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:
  - Discontinuation of study drug prior to or in the Week 24 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  - Discontinuation of study drug prior to or in the Week 24 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  - Missing data during the window but on study drug

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

6.2.1.2. Percentage of Participants with HIV-1 RNA < 400 copies/mL at Week 24 as Determined by the US FDA-defined Snapshot Algorithm

The same definition as outlined in Section 6.2.1.1 will be applied, with the following exception:

- 50 copies/mL will be replaced with 400 copies/mL

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

The same definition as outlined in Section 6.2.1.1 will be applied, with the following exception:

- Week 24 will be replaced with Week 48
  - The analysis window at Week 48 is defined as from Study Day 308 to Study Day 377.

6.2.1.4. Percentage of Participants with HIV-1 RNA < 400 copies/mL at Week 48 as Determined by the US FDA-defined Snapshot Algorithm

The same definition as outlined in Section 6.2.1.3 will be applied, with the following exception:

- 50 copies/mL will be replaced with 400 copies/mL

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 and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

6.2.2.2. Percentage of Participants with HIV-1 RNA < 400 copies/mL at Week 24 as Determined by the US FDA-defined Snapshot Algorithm

This endpoint is applicable for Cohort 1 only. All required analyses for this endpoint have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR

6.2.2.3. 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 and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

6.2.2.4. Percentage of Participants with HIV-1 RNA < 400 copies/mL at Week 48 as Determined by the US FDA-defined Snapshot Algorithm

This endpoint is applicable for Cohort 1 only. All required analyses for this endpoint have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR

6.2.2.5. Change from Baseline in HIV-1 RNA Values

This endpoint is applicable for Cohort 1 only.

HIV-1 RNA (log10 copies/mL) data will be summarized using observed, on-treatment data (ie, data collected up to 1 day after the last dose date).

Absolute values and changes from baseline in HIV-1 RNA (log10 copies/mL) at each visit will be summarized descriptively (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and overall 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 will be plotted.

The absolute values of HIV-1 RNA (log10 copies/mL) at each visit will also be listed.

6.2.2.6. Change from Baseline in CD4 Cell Counts and Percentages

CD4 cell counts and CD4% data will be summarized using observed, on-treatment data (ie, data collected up to 1 day after the last dose date).

Absolute values and changes from baseline in CD4 cell count (cells/μL) and CD4% at each visit will be summarized descriptively (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and overall 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 will be plotted.

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

6.3. Other Efficacy Endpoints

6.3.1. Analysis of Other Efficacy Endpoints

6.3.1.1. Percentage of Participants with HIV-1 RNA < 50 copies/mL

All required analyses for this endpoint using the Missing = Failure (M = F) method for imputing missing HIV-1 RNA values have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

The number and percentage of participants with HIV-1 RNA < 50 copies/mL will be analyzed by cohort and overall for each visit using the following method for imputing missing HIV-1 RNA values:

- Missing = Excluded (M = E)
  - In this approach, all missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit.

For M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL not detectable

    - < 20 copies/mL detectable
    - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL

In the M = E analyses, the 95% CI of the proportion of participants with HIV-1 RNA < 50 copies/mL will be constructed using the Clopper-Pearson exact method.

Furthermore, the proportion of participants with HIV-1 RNA < 50 copies/mL over time will be plotted for the M = E analyses.

6.3.1.2. Percentage of Participants with HIV-1 RNA < 400 copies/mL

This endpoint is applicable for Cohort 1 only. All required analyses for this endpoint using the M = F method for imputing missing HIV-1 RNA values have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR

The number and percentage of participants with HIV-1 RNA < 400 copies/mL will be analyzed by cohort for each visit using the M=E method for imputing missing HIV-1 RNA values. For M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized:

- < 400 copies/mL
- ≥ 400 copies/mL

In the M = E analyses, the 95% CI of the proportion of participants with HIV-1 RNA < 400 copies/mL will be constructed using the Clopper-Pearson exact method.

The proportion of participants with HIV-1 RNA < 400 copies/mL over time will be plotted for the M = E analyses.

6.4. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

Analysis of safety data will be conducted on the Safety Analysis Set, unless otherwise specified in the following sections. The treatment-emergent (TE) period is defined as the time period from the first dose date of study treatment up to and including 30 days after the last dose of study treatment.

All safety data during the TE period will be summarized by cohort and overall as defined in Section 3.2.. Data for the pretreatment period will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead 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:

- Any AEs that start during the TE period defined at the beginning of Section 7 (ie, with onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug)

- Any AE leading to premature discontinuation of study drug.

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 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 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

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 overall. Treatment-emergent deaths observed in the study will also be included in this summary. Treatment-emergent death refers to a death that occurred between the first dose date and the last dose date plus 30 days (inclusive).

In addition, a brief, high-level summary of TEAEs up to the nominal Week 24 visit will also be provided by cohort 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 will also be done for the nominal Week 48 visit. Cumulative TEAE summaries by cohort and overall will also be presented.

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

- TEAEs

- TEAEs by maximum severity
- TEAEs with Grade 3 or 4
- TEAEs with Grade 2 or 3 or 4
- TE study drug-related AEs
- TE study drug-related AEs by maximum severity
- TE study drug-related AEs with Grade 3 or 4
- TE study drug-related AEs with Grade 2, 3, or 4
- TE SAEs
- TE study drug-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to 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. For summaries by severity grade, the worst severity will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs 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, indicating whether the event is TE
- All AEs up to nominal Week 48, indicating whether the event TE
- All SAEs
- All study drug-related SAEs
- All Deaths

- All SAEs leading to death (ie, outcome of death)
- All AEs with severity of Grade 3 or 4
- All AEs with severity of Grade 2, 3, or 4
- All AEs leading to premature discontinuation of study drug

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. Events that 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 study protocol amendment 7 Appendix 6.

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 overall by TEAE of interest category and PT. A by-participant listing of fracture events will also 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 in the TE period defined at the beginning of Section 7.

A by-participant listing for laboratory test results will be provided by cohort, 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.

The laboratory test reference ranges for hematology, serum chemistry (including liver-related and bonerelated evaluations), urinalysis, and CD4 cell count and percentage will also be listed.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort and overall for the following laboratory categories and tests (in conventional units):

- Hematology: Hemoglobin (g/dL); Hematocrit (%); Mean Corpuscular Hemoglobin (pg); Mean Corpuscular Hemoglobin Concentration (g/dL); Mean Corpuscular Volume (fL); Red Blood Cells (x10^6/uL); Platelet Count (x10^3/uL); White Blood Cells (x10^3/uL); Absolute Neutrophils (x10^3/uL); Absolute Lymphocytes (x10^3/uL); Absolute Monocytes (x10^3/uL); Absolute Basophils (x10^3/uL); Absolute Eosinophils (x10^3/uL)

- Chemistry: Sodium (mEq/L); Potassium (mEq/L); Chloride (mEq/L); Bicarbonate (mEq/L); Phosphorus (mg/dL); Calcium Corrected for Albumin (mg/dL); Magnesium (mg/dL); Serum Creatinine (mg/dL); $eGFR_{Schwartz}$ (mL/min/1.73m^2); Uric Acid (mg/dL); Blood Urea Nitrogen (mg/dL); Creatinine Kinase (U/L); Albumin (g/dL); Total Protein (g/dL); Alkaline Phosphatase (ALP, U/L); Alanine Aminotransferase (ALT, U/L); Aspartate Aminotransferase (AST, U/L); Total Bilirubin (mg/dL); Direct Bilirubin (mg/dL); Indirect Bilirubin (mg/dL)

as follows:

- Baseline values

- Values at each postbaseline visit

- Change from baseline at each postbaseline visit

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

Median (Q1, Q3) change from baseline values for the following laboratory tests: serum creatinine (mg/dL) and $eGFR_{Schwartz}$ (mL/min/1.73m^2) will be plotted using a line plot by cohort and visit.

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

Cystatin C

Cystatin C was collected for Cohorts 1 and 2 only. All required analyses for this laboratory parameter have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 2 CSR
- Cohort 2: Interim Analysis 4 CSR

Renal Safety Assessments

All required analyses for urine renal safety markers have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 4 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

Metabolic Assessments

For the lipid panel and glucose, only those measurements under fasting status will be summarized:

- Total Cholesterol (mg/dL); Low Direct Density Lipoprotein (mg/dL); High Density Lipoprotein (HDL, mg/dL); Total Cholesterol to HDL Ratio; Triglycerides (mg/dL); Glucose (mg/dL)

Bone Safety Assessments

Serum bone safety markers include the following:

- Bone Specific Alkaline Phosphatase (ug/L), N-telopeptide (nmol BCE/L) (Cohorts 1 and 2 only), C-telopeptide (CTx, ug/L) (Cohorts 1 and 2 only), Osteocalcin (ng/mL) (Cohorts 1 and 2 only), Procollagen Type 1 N-Terminal Propeptide (P1NP, ng/mL) (Cohorts 1 and 2 only), Parathyroid Hormone (PTH, pg/mL), 25-OH Vitamin D (ng/mL) and 1, 25-OH Vitamin D (pg/mL)

Urine bone safety markers are collected for Cohorts 1 and 2 only and include the following:

- Bicarbonate (mEq/L), N-telopeptide (nmol BCE/L)

Percentage change from baseline at each postbaseline visit will also be included in addition to the descriptive statistics outlined at the beginning of this section.

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.

Maximum postbaseline grade, instead of TE grade, for nonfasting glucose will be summarized, as nonfasting glucose was not assessed at baseline visit; therefore, it cannot be determined if an abnormality is TE or not.

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

If there is any laboratory toxicity grading scale overlapping with normal reference ranges (eg, Grade 1 scale overlaps with normal reference ranges), laboratory values within normal range will not be graded except lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities (TELAs) are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point during the TE period defined at the beginning of Section 7. 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.

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 TELAs will be provided by laboratory test, cohort, and overall; participants will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Graded TELAs
- Grade 3 or 4 TELAs

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the TE period defined at the beginning of Section 7.

A by-participant listing of graded TELAs and Grade 3 or 4 TELAs will be provided by cohort, 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.

7.2.3. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized by cohort and overall using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- AST: (a) > 3× of the upper limit of normal (ULN); (b) > 5 × ULN; (c) > 10 × ULN; (d) >20 × ULN
- ALT: (a) > 3 × ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN; (b) > 2 × ULN
- ALP: > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN; (b) > 2 × ULN
- AST or ALT > 3 × ULN, ALP < 2 × ULN, and associated with total bilirubin > 2 x ULN

The summary will include data from all postbaseline visits during the TE period defined at the beginning of Section 7. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. Participants who met the most severe category will also be counted for the less severe categories. For 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 with nonmissing postbaseline values of 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 × ULN will also be listed.

7.3. Bone Mineral Density Evaluations

The Spine and TBLH DXA Analysis Sets will be the primary analysis sets for the BMD assessments for spine and TBLH, respectively.

Bone mineral density will be evaluated in 2 body sites: spine and TBLH. Bone mineral density standard Z-score will be computed based on a chronological age-matched population of the same sex and ethnicity. Bone mineral density height-age Z-score will be generated by substituting

height-age for chronological age, where height-age is height-matched age calculated using the Centers for Disease Control (CDC) Year 2000 Length and Stature-for-age charts published on the following CDC website:

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

If a participant's height exceeds the height chart, the participant will be considered and adult and 20 years will be used as their height-age. The BMD Z-scores (standard and height-age) will be calculated for the 2 body sites (ie, spine and TBLH).

The BMD data will be summarized up to and including 30 days after the last dose of study treatment.

Descriptive statistics will be provided at each visit by cohort and overall for BMD data (ie, spine and TBLH) as follows:

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

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

- Baseline value
- Value at each postbaseline visit
- Change from baseline to each postbaseline visit

The number and percentage of participants with at least 4% decline in either spine or TBLH BMD from baseline to each postbaseline visit will be summarized by cohort and overall.

Shift tables of the clinical BMD (ie, spine and TBLH) status at baseline versus postbaseline visits will be presented by cohort and overall. Clinical BMD status will be stratified into 2 categories using the BMD Z-scores (standard and height-age: Z-scores > -2 vs. Z-scores ≤ -2 {Gordon 2008}. The shift will be from > -2 to ≤ -2.

A listing of participants with at least 4% decline from baseline in either spine or TBLH BMD at any postbaseline visit will be provided. BMD values, Z-scores (standard and height-age), and height-age will be listed. A listing of participants with BMD (spine and/or TBLH) Z-score (standard and height-age) ≤ -2 at any postbaseline visit and > -2 at baseline will also be provided.

7.4. 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 CDC website:

- For participants ≥ 2 years, CDC's 2000 growth charts for those without obesity and CDC's 2022 Extended BMI-for-Age growth charts for those with obesity are used
- For participants < 2 years, World Health Organization (WHO) growth charts are used

The methods and SAS program published on the following CDC websites will be applied to calculate the Z-score:

- https://www.cdc.gov/growthcharts/2000GrowthChart-US.pdf
- https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5909a1.htm
- https://www.cdc.gov/nchs/data/series/sr_02/sr02-197.pdf
- https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas.html
- https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas-who.html

Descriptive statistics will be provided by cohort and overall, for body weight, body weight Z-score, height, height Z-score, BMI, BMI Z-score, and vital signs (blood pressure, pulse, respiration rate, and temperature) as follows:

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

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

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

A by-participant listing of vital signs will be provided by cohort, participant ID number, and visit in chronological order. Body weight, body weight Z-score, height, height Z-score, BMI, and BMI Z-score will be listed separately.

7.5. 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.

Summaries will be based on the Safety Analysis Set. A participant reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

No formal statistical testing is planned.

7.5.1. Non-Study Drug Antiretroviral Medications

For the purposes of analysis, any medication with an end date on or one day before the first dosing date of study drug will be considered a non-study drug ARV medication received immediately prior to the first dose date of study drug (or pre-switch ARV used). Any medication with a start date prior to or on the first dosing date of study drug and (a) continued to be taken after the first dosing date or (b) with a completely missing stop date will be considered a non-study drug ARV medication received immediately prior to the first dose date of study drug (or pre-switch ARV used).

Prior non-study drug ARV medications received immediately prior to the first dose date of study drug will be summarized by ARV category and preferred name using the number and percentage of participants for each cohort and overall.

All prior and concomitant non-study drug ARV medications will be provided in a by-participant listing sorted by cohort, participant ID number, and administration date in chronological order.

7.5.2. Non-Antiretroviral Medications

Non-antiretroviral medications are medications other than per-protocol study drugs and ARV medications.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date or started after the first dosing date 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.

Use of concomitant non-ARV medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each cohort and overall.

All prior and concomitant non-ARV medications (other than per-protocol study drugs and ARV medications) will be provided in a by-participant listing sorted by cohort, participant ID number, and administration date in chronological order.

7.6. Electrocardiogram Results

All required analyses have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 4 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

7.7. Tanner Stage Assessments

Tanner stage was assessed for participants ≥ 6 years of age at protocol-specified visits or until participants reached Tanner Stage 5

Shifts in Tanner stages (breasts, pubic hair, and maximum stage for female; genitalia, pubic hair, and maximum stage for male) from baseline at each postbaseline visit will be summarized by sex, cohort, and overall using frequency count and percentage. The denominator for percentage will be the number of participants with nonmissing values in a given baseline category.

A by-participant listing for Tanner stage results will also be presented.

7.8. Palatability and Acceptability Assessments

All required analyses have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim Analysis 4 CSR
- Cohort 2: Interim Analysis 4 CSR
- Cohort 3: Interim Analysis 5 CSR

7.9. Other Safety Measures

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

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

7.10. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Analyses Related to Intensive PK Sampling

All required analyses have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1 Part A: Interim Analysis 1 CSR
- Cohort 2 Part A: Interim Analysis 3 CSR
- Cohort 3: Interim Analysis 5 CSR

8.2. PK Analyses Related to Sparse PK Sampling

All required analyses for sparse PK sampling have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim 4 CSR
- Cohort 2: Interim 4 CSR
- Cohort 3: Interim 5 CSR

8.3. PK Analyses Related to PBMC

All required analyses have already been reported and will not be repeated for the Final Analysis CSR.

- Cohort 1: Interim 2 CSR
- Cohort 2: Interim 4 CSR
- Cohort 3: Interim 5 CSR

8.4. 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

nQuery Advisor® Version 6.0 (Statistical Solutions Ltd, Cork, Ireland)

SAS® Version 9.4 (SAS Institute Inc., Cary, NC)

Phoenix WinNonlin® Version 8.2 (Pharsight Corporation, Princeton, NJ, USA.)

11. SAP REVISION

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

12. APPENDICES

12.1. Appendix 1: Schedule of Assessments

Study Procedures	Screening[a]	Baseline (Day 1)	Week 1 (Day 7)	Week 2[b]	Intensive PK[c]	End of Week[b]								Post-Week 48[b] Every 12 weeks[gg]	30-Day Follow-up[d]	ESDD[e]
						4	8	12	16	24	32	40	48			
Assent/Informed Consent	X															
Medical History	X															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X								X			X			X
Symptom-Directed Physical Exam[g]			X	X	X	X	X	X	X		X	X		X	X	
Height	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Tanner Stage Evaluations[h]		X								X			X	X		
12-lead ECG - performed supine	X															
HIV-1 Genotype[i]	X															
Hematology Profile[j]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[k]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Screening[a]	Baseline (Day 1)	Week 1 (Day 7)	Week 2[b]	Intensive PK[c]	End of Week[b] 4	8	12	16	24	32	40	48	Post-Week 48[b] Every 12 weeks[gg]	30-Day Follow-up[d]	ESDD[e]
Metabolic Assessments[l]	X[ff]	X[ee]								X			X	X		
Plasma HIV-1 RNA[m]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample[n]		X[ee]				X[z]	X	X	X	X	X[ee]	X	X	X		X
Whole Blood Sample (Cohort 3)	X															
CCI																
HBV and HCV Serologies	X															
Urinalysis	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Estimated Glomerular Filtration Rate[o]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CCI																
Serum Pregnancy Test[q]	X															
Urine Pregnancy Test[q]		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Dispense Dosing Diary (for Part A subjects, inclusive of Cohort 3)			X[ff]	X												
Review Dosing Diary (For Part A subjects,					X											

Study Procedures	Screening[a]	Baseline (Day 1)	Week 1 (Day 7)	Week 2[b]	Intensive PK[c]	End of Week[b] 4	8	12	16	24	32	40	48	Post-Week 48[b] Every 12 weeks[gg]	30-Day Follow-up[d]	ESDD[e]
inclusive of Cohort 3)																
Single PK Sampling[r]						X[z]	X	X	X		X[dd]	X[dd]				X
Trough PK Sample[s]			Xee	Xee		X[ff]				X			X			
Intensive PK Sampling[t]					X											
CCI																
DXA Scan (Lumbar spine & Total Body)[v]		X								X			X	X		
Bone Safety[w]	X[ff]	X[ee]					X	X		X			X	X		
Urine Renal Safety[x]	X[ff]	X[ee]					X	X		X			X			
Study Drug Dispensation		X				X	X	X	X	X	X	X	X	X		
In-clinic Dosing[y]		X	X	X		X		X		X			X			
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X		X
Palatability and Acceptability Assessment		X[bb]				X[bb]				X[aa, bb]	X[aa]	X[aa]	X[aa, bb]	X[aa]	X[cc]	X[cc]

a Evaluations to be completed within 35 days prior to Baseline (or 42 days for participants who require repeat testing of the HIV-1 genotype).
b All study visits are to be scheduled relative to the Baseline/Day 1 visit date. Visit windows are ± 2 days of the protocol-specified visit date from Week 2 through Week 8, ± 4 days of the protocol-specified visit date from Week 12 through Week 48, and ± 6 days of the protocol-specified visit date post-Week 48, unless otherwise specified.
c Part A participants only, inclusive of Cohort 3. The Intensive PK evaluation will occur at the Week 4 (Cohorts 1 and 2) or Week 2 (Cohort 3) visit. For the purpose of scheduling the Intensive PK visit, a + 7 days window may be used. If the participant has already dosed prior to the Intensive PK evaluation visit or is not in a fasted state, the Intensive PK assessments must not be completed. The participant should be instructed to return in a fasted state within 7 days of their Week 4 (Cohorts 1 and 2) or Week 2 (Cohort 3) visit for the Intensive PK visit.

d Only required for those participants not enrolling in the extension phase of the study 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 Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.

e ESDD visit should occur within 72 hours of last dose of study drug.

f Vital signs include blood pressure, pulse, respiration rate, and temperature.

g Symptom-directed physical examinations performed as needed.

h Tanner assessments will be performed on participants ≥ 6 years of age and no longer be performed once a participant has been documented as Tanner Stage 5.CCI [redacted]

i Analysis for reverse transcriptase, protease and integrase resistance will be done at Screening. The investigator must have received the results from the Screening genotype before proceeding with the Baseline visit. (Cohort 1 only)

j CBC with differential and platelet count.

k Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, cystatin C (Cohorts 1 and 2; Baseline, Weeks 2 [Cohort 1 only], 4, 24, and 48), total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, CPK, and uric acid.

l Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). Metabolic assessments will be performed every 48 weeks.CCI [redacted]

m For Part A participants (inclusive of Cohort 3), back-up samples will not be collected at Weeks 1, 2, and 4 visits for Cohort 1 and at Weeks 1 through 16 for Cohorts 2 and 3. For Part B participants, back-up samples will be collected at all visits.

n CCI [redacted]

o Estimated GFR using Schwartz Formula (mL/min/1.73m^2) = k × L/S_{cr}.

p CCI [redacted]

q Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test at any visit.

r Cohort 1: a timed random PK sample collected at Week 4 (Cohort 1 Part B subjects only) and Week 12 (all Cohort 1) between 0.24-4 hours post-dose. A random PK sample collected at all other visits through Week 48. Cohort 2: a timed random PK at Week 12 between 0.24-4 hours post-dose and Week 8 and Week 16 random single PK sample. Cohort 3: a random timed PK sample collected between 0.25 and 4 hours post-dose at Week 8, 12, and 16.

s Participants must come into the clinic without taking their dose of E/C/F/TAF STR and participants should fast overnight (a minimum of 8 hours). A trough (20 to 24 hours post-dose) plasma PK sample will be collected at Weeks 1, 2, and 24 for participants in Cohort 1 and 2 and Week 48 for Cohort 1 only. For participants in Cohort 3, a trough sample will be collected at Weeks 4 and 24.

t Part A participants only, inclusive of Cohort 3. Intensive PK sampling will be performed on Week 4 (Cohorts 1 and 2) or Week 2 (Cohort 3). For the purpose of scheduling the Intensive PK visit a + 7 days window may be used. If the participant has already dosed prior to the Intensive PK visit or is not in a fasted state, the Intensive PK assessments must not be completed. The participant should be instructed to return within four days for the Intensive PK visit. If dosing non-compliance is identified on or prior to the Intensive PK visit, the Intensive PK assessments must not be completed. The participant should be counseled regarding proper dosing and asked to return for the Intensive PK visit no sooner than three days following compliant dosing and no later than Week 4 + 7 days. Please refer to the PK/PBMC manual for sample collection and processing details.

u CCI [redacted]

v DXA scans to be performed in all eligible participants prior to study drug administration at Baseline. DXA scan also to be performed Weeks 24 and 48 (± 10 days). CCI [redacted].

w For Cohorts 1 and 2, bone safety including:
Serum: bicarbonate, N-telopeptide, C-telopeptide (CTX), osteocalcin, procollagen type 1 N-terminal propeptide (P1NP)
Urine: bicarbonate, N-telopeptide

x For all cohorts, bone safety including:

Serum: bone specific alkaline phosphatase, parathyroid hormone (PTH), 25OH Vitamin D and 1, 25OH Vitamin D

y Urine Renal Safety including: urine chemistry, retinol binding protein, and beta-2-microglobulin.

z All participants will be given their dose of E/C/F/TAF STR with food. For those participants that take their medication in the evening, the in-clinic dosing will not be performed.

aa Cohort 1 Part B participants only

bb To be performed for all Cohort 1 participants currently on study at their next scheduled visit.

cc To be performed at Baseline and Week 4 for all Cohort 2 participants and at Baseline, Weeks 4, 24, and 48 for all Cohort 3 participants enrolled.

dd To be performed at ESDD or 30-Day Follow-Up visit for either Cohort 1 or 2, as applicable.

ee Cohort 1 participants only

ff Cohort 1 and 2 participants only

gg Cohort 3 participants

CCI [redacted]

12.2. Appendix 2: Data Collection of Disaster or Public Health Emergency Data

This appendix describes the clinical trial site collection of Disaster or Public Health Emergency 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 Disaster or Public Health Emergency supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the Disaster or Public Health Emergency. 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 (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table 12-1 for eg for COVID-19 pandemic). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit" will be assigned as follows:

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

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

iii. Otherwise result is missing

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

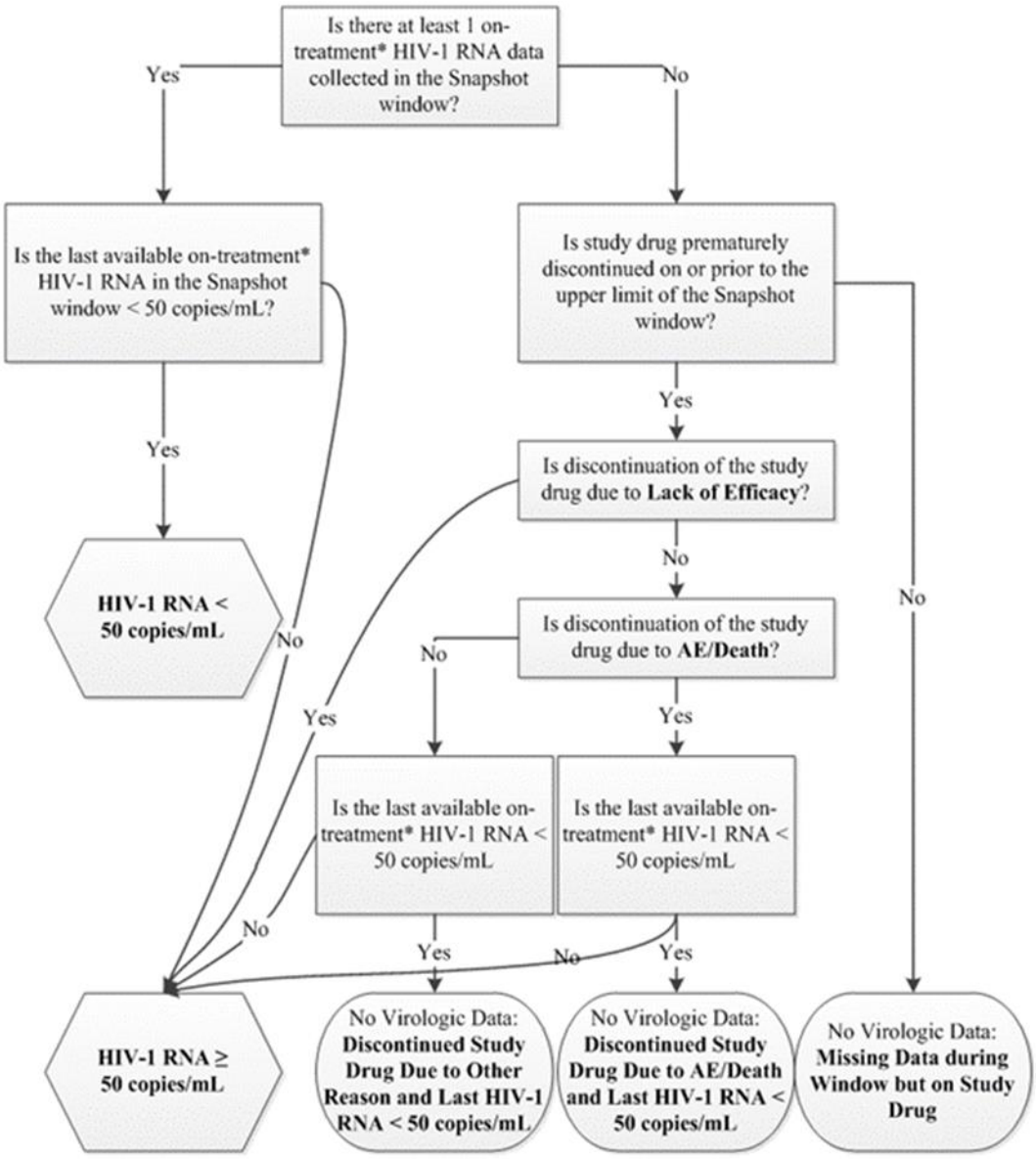
Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	REMOTELY
LOCKDOWN	TELEMEDICINE
QUARANTINE	TELECONSULTATION

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

12.3. Appendix 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 date.

12.4. Appendix 4: Laboratory Values

Calcium Corrected for Albumin

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

$$\text{Calcium Corrected for Albumin } (mg/dL) =$$

$$\textit{Serum calcium (mg/dL)} + (0.8 \times [4.0 - \textit{Albumin } (g/dL)])$$

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

Estimated Glomerular Filtration Rate

The following formula will be used to calculate $eGFR_{Schwartz}$:

$$\text{eGFR } (\text{ml/min/1.73m}^2) = \text{k} \times \text{L/SCr}$$

where k is the proportionality constant (0.55 for children to 12 years old; 0.55 for adolescent females ≥ 12 years old; 0.70 for adolescent males ≥ 12 years old); L is height (cm); SCr is serum creatinine (mg/dL).

12.5. Appendix 5: Programming Specifications

General Conventions

1) AGE is 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 who are enrolled and never dosed with study drug, AGE will be calculated based on the date of enrollment.

2) All screened participants refers to all participants who are screened (ie, with nonmissing screening date) and have a screening number. For summarization, the same participant is counted only once. Date of birth and other demographic information such as sex, race, and ethnicity will be used for identifying unique screened participants.

3) 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 and were not enrolled. In addition, there are participants who "Met All Eligibility Criteria" ie, those who were screened but not enrolled. These are participants who answered "No" to "Will Subject be Enrolled in Study" in the Enrollment eCRF.

4) Participants in the All Enrolled Analysis Set are defined as participants enrolled in the study. IWRSRAND is the source to determine whether a participant is enrolled (ie, participant with non-missing ENROLLDTN in the IWRSRAND dataset), and confirmed by the ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

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

6) BMI and BSA

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

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

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

c) 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)

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

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

7) Please note, "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%.

8) 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.

If the date of last dose is missing (ie, only year of last dose is known or completely missing due to lost to follow-up), the maximum of study drug start dates and end dates, clinical visit dates, and laboratory visit dates excluding the 30-day follow-up visit will be used to impute the last dose date.

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.

9) Listing for US FDA-defined snapshot outcome:

In addition to flagging the values of HIV-1 RNA < 50 or ≥ 50 copies/mL for virologic outcomes, flag the last available HIV-1 RNA value while on treatment for the following categories:

— HIV-1 RNA ≥ 50 copies/mL - discontinued study drug due to AE or death and last available HIV-1 RNA ≥ 50 copies/mL

— HIV-1 RNA > 50 copies/mL - discontinued study drug due to other reason* and last available HIV-1 RNA ≥ 50 copies/mL

— No virologic data - discontinued study drug due to AE or death and last available HIV-1 RNA < 50 copies/mL

— No virologic data - discontinued study drug due to Other reason* and last available HIV-1 RNA < 50 copies/mL

Note: * Other reasons include participants who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

10) For HIV-1 RNA M = F, 'have not reached the upper limit of that analysis window for the corresponding visit' refers to: the latest lab collection date – first dose date + 1 < the upper limit of the analysis window for a visit.

M = F when

— The participant has a visit after the missing value.

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

— 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

— For ongoing participants, HIV-1 RNA is missing and upcoming visit has not happened yet (excluding ongoing subjects who have not reached the upper limit of the analysis window for the corresponding visit).

— 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 a TEAE if end date meets any of the criteria specified in 3) above.

12) TEAEs up to the nominal Week 24 visit

Any TEAE onset date on or before the nominal Week 24 visit date will be included.

If TEAE onset date is partial, the onset date is on or before the month and year (or year alone) of the nominal Week 24 visit, it will be included. If the TEAE onset date is completely missing, it will be included as well.

If a participant discontinued the study before Week 24 visit, all TEAEs will be included.

13) TEAEs up to the nominal Week 48 visit

Any TEAE onset date on or before the nominal Week 48 visit date will be included.

If TEAE onset date is partial, the onset date is on or before the month and year (or year alone) of the nominal Week 48 visit, it will be included. If the TEAE onset date is completely missing, it will be included as well.

If a participant discontinued the study before Week 48 visit, all TEAEs will be included.

14) Graded Laboratory Abnormalities Summary

The following labels will be used for TELAs and Grade 3 or 4 TELAs summary tables:

Battery	Laboratory Test Label	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)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	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)

Battery	Laboratory Test Label	Toxicity Direction	Laboratory Test Label Used in t-labtox Table
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Dipstick)
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative)

For hematuria grading, the laboratory reports both dipstick results (urine blood test with values of 1+, 2+, etc) and quantitative results (urine RBC test with a unit of /HPF), only summarize toxicity grades of the quantitative (urine RBC) results, but list the grades from both tests.

15) 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:

- second generation (mmol/L) = (third generation - 0.0626)/0.882
- 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

16) Direct Bilirubin: Conversions between first and second generations

Direct Bilirubin was analyzed by 2 different assays in the study: first generation (RCT29) and second generation (RCT6657). Samples collected at earlier visits were analyzed using Direct Bilirubin first generation assay. Samples collected after 06-Jan-2025 were analyzed using Direct Bilirubin second generation assay. The conversion formulas are as follow:

— Converting to first generation:

- First Generation (µmol/L) = (Second Generation - 2.832) / 1.032
  - Any converted results below the limit of quantification (<2 umol/L) for the first generation assay will be assigned a value of <2 umol/L. This includes records where the second generation result is "<1.4 umol/L".

— Converting to second generation:

- When converting first generation to second generation, the reported first generation result must first be assessed:

a) If first generation value is below 10 µmol/L, then the conversion formula is:
   - Second Generation (µmol/L) = (1.181 x First Generation) + 0.492
     i. If first generation result is below the limit of quantification (<2 umol/L), then the second generation result will be assigned "<2.9 umol/L".
     ii. If the calculated second generation result is greater than the result for Total Bilirubin, then the second generation result will be assigned the same value as Total Bilirubin.

b) If first generation value is equal to or above 10 µmol/L, then the conversion formula is:
   - Second Generation (µmol/L) = (1.032 x First Generation) + 2.832
     i. If the calculated second generation result is greater than the result for Total Bilirubin, then the second generation result will be assigned the same value as Total Bilirubin.

For this analysis, since the majority of the Direct Bilirubin samples were analyzed by first generation assay, only conversion from second generation to first generation was requested.

For the analysis of toxicity grade for Direct Bilirubin: 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 (BILDTOX) for "Direct Bilirubin for Toxicity" will be generated to pool the records from first generation and second generation to derive TE toxicity grades, maximum postbaseline toxicity grades, etc

17) Indirect Bilirubin: Conversions between first and second generations

a) If Direct Bilirubin was converted to first generation:

- First Generation Indirect Bilirubin (umol/L) = Total Bilirubin – First Generation Direct Bilirubin

  - If the result for Total Bilirubin or first generation Direct Bilirubin is blank or missing, then the result for first generation Indirect Bilirubin will be blank.

  - For any instances where first generation Direct Bilirubin is "<2 umol/L", the first generation Indirect Bilirubin calculation should equal the Total Bilirubin result (in umol/L) preceded by "<". If the Total Bilirubin result already has a "<", the Indirect Bilirubin result should match.

b) If Direct Bilirubin was converted to second generation:

- Second Generation Indirect Bilirubin (umol/L) = Total Bilirubin – Second Generation Direct Bilirubin

  - If the result for Total Bilirubin or second generation Direct Bilirubin is blank or missing, then the result for second generation Indirect Bilirubin will be blank.

  - For any instances where second generation Direct Bilirubin is "<2.9 umol/L", the second generation Indirect Bilirubin should equal the Total Bilirubin result (in umol/L) preceded by "<". If the Total Bilirubin result already has a "<", the Indirect Bilirubin result should match.

18) PK parameters (if applicable) at the individual participant level should be displayed with the following reported number of decimal places:

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

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

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

— NPOINTS: 0 decimal place

— PK concentration data will be reported with 1 decimal place.

19) Unit conversion for PK parameters of CLss/F and Vz/F

a) CLss/F (L/h): 1 mL/h ÷ 1000 = 1/1000 x L/h

b) Vz/F (L): 1 mL ÷ 1000 = 1/1000 x L

20) Details on the lower LOQ for the PK analytes of interest (plasma and PBMC) are provided below.

Analyte	Lower limit of quantitation (ng/mL)
EVG	20.0
COBI	5.0
FTC	5.0
TAF	1.0
TFV	0.3
TFV-DP	1.8

21) "On-treatment" data refers to data collected up to 1 day after the last dose date.

22) Extrapolation in DXA data

Clario processes DXA data for clinical trials of both Hologic and GE Lunar manufactured DXA scanners. Reference population data by manufacturer, gender, age, and ethnicity are provided and supported by the manufacturers; however, they do not always cover the entire range of study populations seen within the clinical trials. To provide comparable data across all subjects within a given trial, Clario has extrapolated existing reference data to fill the missing ranges from the current references.

See tables below for the calculations and assumptions made to produce the extrapolated references for each scanner type.

Manufacturer	Anatomy	Gender	Ethnicity	Age
Hologic	AP Spine L1-L4	Female	White	0-3
Hologic	AP Spine L1-L4	Female	Black	0-6
Hologic	AP Spine L1-L4	Female	Hispanic	0

Manufacturer	Anatomy	Gender	Ethnicity	Age
Hologic	AP Spine L1-L4	Male	White	0-3
Hologic	AP Spine L1-L4	Male	Black	0-6
Hologic	AP Spine L1-L4	Male	Hispanic	0

Manufacturer	Anatomy	Gender	Ethnicity	Age
GE Lunar	AP Spine L1-L4	Female	White	0-4
GE Lunar	AP Spine L1-L4	Female	Black	0-4
GE Lunar	AP Spine L1-L4	Male	White	0-4
GE Lunar	AP Spine L1-L4	Male	Black	0-4

Manufacturer	Anatomy	Gender	Ethnicity	Age
Hologic	Total Body Less Head	Female	White	0-7 and 20-25
Hologic	Total Body Less Head	Female	Black	0-7 and 20-25
Hologic	Total Body Less Head	Female	Hispanic	0-7 and 20-25
Hologic	Total Body Less Head	Male	White	0-7 and 20-25
Hologic	Total Body Less Head	Male	Black	0-7 and 20-25
Hologic	Total Body Less Head	Male	Hispanic	0-7 and 20-25

Manufacturer	Anatomy	Gender	Ethnicity	Age
GE Lunar	Total Body Less Head	Female	White	0-7 and 20-25
GE Lunar	Total Body Less Head	Female	Black	0-7 and 20-25
GE Lunar	Total Body Less Head	Female	Hispanic	0-7 and 20-25
GE Lunar	Total Body Less Head	Male	White	0-7 and 20-25
GE Lunar	Total Body Less Head	Male	Black	0-7 and 20-25
GE Lunar	Total Body Less Head	Male	Hispanic	0-7 and 20-25

Note: The “AP Spine L1-L4” and “Total Body Less Head” under column “Anatomy” do not correspond to any specific Spine or Total Body parameters, they are considered as reference document names only for Clario.

Based on DXA Data Transfer Specification Reference Table 4 “Manufacturer’s T-Scores and Z-Score” and above tables, derive extrapolation flags following below steps:

(1) Calculate age and height-age using floor() function;

(2) Derive extrapolation flag for Z-score using age, and extrapolation flag for height-age Z-score using height-age from (1);

(3) If a participant is Hispanic, use Hispanic reference in above tables regardless of race category; if a participant is not Hispanic, race category of “Other” and “Asian” defaults to ‘White’ for both Hologic and GE Lunar.

(4) For both Hologic and GE Lunar:

(a) All Z-scores of SpineL1_L4 and SpineTotalAdequate will have extrapolation flag as Y if age satisfies above tables (based on manufacture, gender, ethnicity)

(b) All Z-scores and of BodyTotal and BodyTotalNoHead will have extrapolation flag as Y if age satisfies above tables (based on manufacture, gender, ethnicity)

(c) All height-age Z-scores and of BodyTotal and BodyTotalNoHead will have extrapolation flag as Y if height-age satisfies above tables (based on manufacture, gender, ethnicity)

(d) All height-age Z-scores will only have extrapolation flag as Y for SpineL1_L4 and SpineTotalAdequate if height-age satisfies above tables (based on manufacture, gender, ethnicity)

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