CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND No.:	111007
EudraCT Number:	2013-002780-26
Clinicaltrials.gov Identifier:	NCT01854775
Indication:	Human immunodeficiency virus type 1 (HIV-1) infection
Protocol ID:	GS-US-292-0106
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 04 February 2013 Amendment 1: 22 March 2013 Amendment 2: 09 January 2015 Amendment 3: 11 August 2016 Amendment 4: 11 June 2018 Amendment 5: 17 August 2018 Amendment 6: 21 February 2020 Amendment 7: 01 June 2021

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PROTOCOL SYNOPSIS

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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
IND Number: **EudraCT Number:** **ClinicalTrials.gov Number:**	111007 2013-002780-26 NCT01854775
Study Centers Planned:	Approximately 15 centers in North America, Africa, and Thailand
Objectives:	**Cohort 1** The primary objectives of this study 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 of this study 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

Cohort 2

The primary objectives of this study 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 weighing ≥ 25 kg

The secondary objectives of this study 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

Cohort 3

The primary objectives of this study 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 of this study 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

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Study Design:

Open-label, multicenter, multi-cohort, single-arm study of the pharmacokinetics, safety, tolerability, and antiviral activity of the E/C/F/TAF STR in HIV-1 infected ARV treatment-naive adolescents and virologically suppressed children.

A total of 50 adolescents (12 to < 18 years of age), and up to 75 children (2 to < 12 years of age) of either sex will be enrolled to receive the E/C/F/TAF STR once daily with food as follows:

Part A

Intensive PK samples will be analyzed once they are available from 18 subjects regardless of age distribution (Cohorts 1 and 2 only).

Cohort 1, Part A: EVG, TAF and COBI exposures will be compared to historical data from adult HIV-1 infected subjects. TAF data will also be compared to HIV-negative subjects from GS-US-292-0103 study. FTC and TFV exposures will be compared to historical data in HIV-infected adults and available data in adolescent subjects.

Cohort 2 Part A and Cohort 3: EVG, TAF, COBI, FTC and TFV exposures will be compared to historical adult data.

EVG and TAF dose confirmation will be established if the 90% CI of geometric mean ratios for AUC in adolescents and children (respectively) versus those in adults are within the equivalency bounds of 70-143%.

Following completion of the Intensive PK visit, subjects will continue to receive the E/C/F/TAF STR and return for scheduled study visits through Week 48.

Cohort 1 (Adolescents 12 to < 18 years of age)

- Eighteen to 24 eligible subjects will be initially enrolled to evaluate the steady state pharmacokinetics, and confirm the dose of the E/C/F/TAF STR.
- Part A will aim to enroll at least 6 subjects 12 to < 15 years of age and at least 6 subjects 15 to < 18 years of age.

- If at least 6 subjects ages 12 to < 15 years and 6 subjects ages 15 to < 18 have not been enrolled at the time of the Intensive PK analysis, Part A enrollment will remain open in order to enroll sufficient subjects to meet the minimum enrollment of the 2 age subgroups.
- Subjects enrolled in Part A will participate in an Intensive PK evaluation at Week 4. Samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing), 5 minutes, 0.25, 0.5, 1, 1.5, 2, 4, 5, 8, and 24 hours post-dose.

Cohort 2 (Children 6 to < 12 years of age and weighing ≥ 25 kg)

- Eighteen to 24 eligible subjects will be initially enrolled to evaluate the EVG and TAF plasma PK and confirm the dose of EVG and TAF.
- Subjects enrolled in Part A will participate in an Intensive PK evaluation at Week 4. Samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours post-dose.

Cohort 3 (Children ≥ 2 years of age and weighing ≥ 14 to < 25 kg)

- Approximately 25 eligible subjects will be initially enrolled to evaluate the EVG and TAF plasma PK and confirm the dose of EVG and TAF.
- Subjects enrolled in Part A will participate in an Intensive PK evaluation at Week 2. Samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 8 hours post-dose.

Part B

Cohort 1 (Adolescents 12 to < 18 years of age)

Screening will be initiated into Cohort 1, Part B following confirmation of EVG and TAF exposure in at least 18 subjects from Cohort 1, Part A. The additional 26 – 32 subjects will be enrolled in Cohort 1, Part B to evaluate the safety, tolerability and antiviral activity of the E/C/F/TAF STR in at least 50 patients, including all subjects enrolled in Cohort 1 (Parts A and B combined).

Cohort 2 (Children 6 to < 12 years of age and weighing ≥ 25 kg)

Screening will be initiated into Cohort 2, Part B based on exposure data from at least 18 subjects from Cohort 2, Part A. The additional 26 – 32 subjects will be enrolled in Cohort 2, Part B to evaluate the safety, tolerability and antiviral activity of the E/C/F/TAF STR in at least 50 patients, including all subjects enrolled in Cohort 2 (Parts A and B combined).

Cohort 3 (Children ≥ 2 years of age and weighing ≥ 14 to < 25 kg)

- No Part B for this cohort. All subjects will be enrolled in Part A and will complete an Intensive PK evaluation.

Number of Subjects Planned:

Cohort 1

50 subjects

Part A: Eighteen to 24 subjects representing 2 age subgroups (at least 6 subjects must be 12 to <15 years of age and at least 6 subjects must be 15 to < 18 years of age)

Part B: Twenty-six to 32 subjects between 12 to < 18 years of age (dependent upon enrollment in Part A)

Cohort 2

50 subjects

Part A: Eighteen to 24 subjects between 6 to < 12 years of age weighing ≥ 25 kg

Part B: Twenty-six to 32 subjects must be 6 to < 12 years of age and weighing ≥ 25 kg (dependent upon enrollment in Part A)

Cohort 3

Approximately 25 subjects ≥ 2 years of age and weighing ≥ 14 to < 25 kg

Target Population:

Cohort 1

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

Cohort 2

Virologically suppressed, HIV-1 infected children (6 to < 12 years of age and screening weight ≥ 25 kg) of either sex with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening on a stable antiretroviral regimen, with no documented history of resistance to any component of E/C/F/TAF STR.

Cohort 3

Virologically suppressed, HIV-1 infected children (≥ 2 years of age and screening weight of ≥ 14 to < 25 kg) of either sex with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening on a stable antiretroviral regimen, with no documented history of resistance to any component of E/C/F/TAF STR.

Duration of Treatment:

48 weeks

After completion of Week 48, all subjects receiving the E/C/F/TAF STR who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study where Gilead will provide E/C/F/TAF STR until:

a) the relevant E/C/F/TAF STR formulation is available for use, other than through the study, in the country in which the subject is enrolled, or

b) Gilead Sciences elects to terminate development of E/C/F/TAF STR in the applicable country.

Diagnosis and Main Eligibility Criteria:

HIV-1 infected subjects who meet the following criteria:

Cohort 1

- Age at Baseline: 12 to < 18 years old
- Weight at Screening: ≥ 35 kg (77 lbs)
- Plasma HIV-1 RNA ≥ 1,000 copies/mL at Screening (Roche COBAS TaqMan v2.0)
- Screening genotype report shows sensitivity to EVG, FTC and TFV (Monogram Biosciences, Inc.)
- Subjects with HIV subtype AE who meet all inclusion/exclusion criteria and who have a non-reportable integrase genotype result may proceed with study enrollment. (For Thailand only)
- No prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission)

Cohort 2

- Age at Baseline: 6 to < 12 years old
- Weight at Screening: ≥ 25 kg (55 lbs)
- Plasma HIV-1 RNA: < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is > 50 copies/mL) for ≥ 6 months prior to Screening on a stable antiretroviral regimen, without documented history of resistance to any component of E/C/F/TAF STR

- Unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viremia, or "blip") and prior to screening is acceptable
- Currently receiving an antiretroviral regimen that has been stable for at least 6 months or has been newly initiated within 6 months for reasons other than virologic failure.

Cohort 3

- Age at Baseline: ≥ 2 years old
- Weight at Screening: ≥ 14 kg (31 lbs) to < 25 kg (55 lbs)
- Plasma HIV-1 RNA: < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is > 50 copies/mL) for ≥ 6 months prior to Screening on a stable antiretroviral regimen, without documented history of resistance to any component of E/C/F/TAF STR
  - Unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viremia, or "blip") and prior to screening is acceptable
- Currently receiving an antiretroviral regimen that has been stable for at least 6 months or has been newly initiated within 6 months for reasons other than virologic failure.

Study Procedures/ Frequency:

All Subjects (All Cohorts unless specified):

At the 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 GFR using the Schwartz formula will be performed.

At Screening, HIV-1 protease, reverse transcriptase and integrase genotype will be analyzed (for Cohort 1 only).

HBV and HCV serologies will be analyzed and supine ECG will be performed.

Blood samples will be collected for full flow cytometry panel testing at Screening, Baseline and Weeks 2 - 48.

Adverse events and concomitant medications will be assessed at each visit.

Subjects will return for study visits at Weeks 1 (Day 7), 2, 4, 8, 12, 16, and then every 8 weeks through Week 48.

Subjects enrolled in Part A will participate in an Intensive PK Evaluation at Week 2 (Cohort 3, all subjects) or Week 4 (Cohorts 1 and 2). Subject diary cards will be provided to all Part A subjects to record administration of study drugs prior to the Intensive PK visit.

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

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

Fasting glucose and lipid panel (total cholesterol, high-density lipoprotein, direct low-density lipoprotein, and triglycerides) will be collected at Baseline, Week 24, and Week 48.

The following serum bone safety parameters will be collected at Screening (Cohort 3), Baseline (Cohorts 1 and 2), Week 8 (Cohort 1 only), and Weeks 12, 24, and 48:

- Cohorts 1 and 2: bicarbonate, N-telopeptide, C-telopeptide, osteocalcin, and procollagen type 1 N-terminal propeptide (P1NP).
- For all cohorts: bone specific alkaline phosphatase, parathyroid hormone, 25OH Vitamin D, and 1,25OH Vitamin D.

The following urine bone safety parameters will be collected at Baseline, Weeks 8, 12, 24, and 48:

- Cohorts 1 and 2: bicarbonate and N-telopeptide.

Urine will be collected for renal safety parameters at Screening (Cohort 3), Baseline (Cohorts 1 and 2), Weeks 8, 12, 24, and 48.

- For all cohorts: urine chemistry, retinol binding protein, and beta-2-microglobulin.

Tanner stage will be assessed for subjects ≥ 6 years of age at Baseline, Weeks 24 and 48 or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

For all cohorts, dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body will be performed at Baseline, Weeks 24 and 48 to measure spine bone mineral density (BMD) and total body BMD.

	Resistance testing will be performed using the RT/PR PhenoSense GT assay, the IN GeneSeq assay, and the IN PhenoSense assay (Monogram Biosciences, Inc.) in subjects who experience suboptimal virologic response or virologic rebound, if HIV-1 RNA is ≥ 400 copies/mL. Palatability and Acceptability assessment will be performed at Baseline and Week 4 for Cohort 2 subjects, and Baseline, Week 4, Week 24, and Week 48 for Cohort 3 subjects. For Cohort 1 subjects currently on study, it will be performed at their next scheduled visit. Subjects who are permanently discontinued from the study before Week 48 and subjects who do not wish to continue on the study after completing Week 48 will be required to return to the clinic 30 days after the completion of study drug for a 30-Day Follow-Up Visit. After Week 48, all subjects receiving E/C/F/TAF STR who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study.
Test Product, Dose, and Mode of Administration:	**Cohorts 1 and 2:** Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg STR administered orally once daily with food **Cohort 3:** Elvitegravir 90 mg/cobicistat 90 mg/emtricitabine 120 mg/ tenofovir alafenamide 6 mg STR low dose tablet administered orally once daily with food
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Adverse events, clinical laboratory tests, Tanner stage assessment (subjects ≥ 6 years of age), selected bone biomarkers, renal safety, and BMD to evaluate the safety and tolerability of the treatment regimen.

Efficacy:

Cohort 1

The efficacy endpoints are:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis
- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) and in CD4+ cell count (cells/µL) and percentage at Weeks 24 and 48

Cohorts 2 and 3

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 by the FDA snapshot analysis
- The change from baseline in CD4+ cell count (cells/µL) and percentage at Weeks 24 and 48

PK:

The following plasma pharmacokinetic parameters will be calculated for EVG, COBI, FTC, TAF and TFV, as applicable: AUC_{tau}, AUC_{last}, C_{tau}, C_{max}, C_{last}, T_{max}, T_{last}, λ_z, CL/F, V_z/F, and $T_{½}$ (where possible)

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Statistical Methods:

PK Analyses

PK parameters (AUC_{tau}, C_{tau}, and C_{max}) of EVG and PK parameters (AUC and C_{max}) of TAF will be summarized and compared to historical adult data. Plasma concentration and parameter data of EVG, COBI, FTC, TAF, and TFV will be summarized using descriptive statistics.

An analysis of variance (ANOVA) using a mixed-effects model for appropriate parallel group design will be fitted to natural-logarithm transformed AUC for TAF and AUC_{tau} for EVG to evaluate whether the exposures of these two analytes achieved in adolescent (Cohort 1) or children (Cohorts 2 and 3) are similar to the exposure achieved in adult subjects. An appropriate adult comparator database will be identified and integrated as historical control data.

For each cohort, two one-sided tests with each performed at an alpha level of 0.05 and a boundary of 70% to 143% will be used for exposure equivalence assessment.

Efficacy Analyses

The percentage of subjects who achieve HIV-1 RNA < 50 copies/mL and < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis algorithm will be summarized by cohort. The 95% confidence intervals will also be presented.

The change from baseline in $\log_{10}$ HIV-1 RNA (Cohort 1 only) and CD4+ cell count and percentage at Weeks 24 and 48 will be summarized by cohort using descriptive statistics.

Sample Size and Power

Cohorts 1 and 2

A minimum of 18 Part A subjects from each cohort compared to 51 HIV-infected adult subjects in GS-US-292-0102 and HIV-negative adult subjects in GS-US-292-0103 combined, will provide 92% power to conclude exposure equivalence of TAF AUC_{last} in adolescent subjects and children, respectively vs in adult subjects, assuming 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 standard deviation of AUC_{last} is 0.37 ng•hr/mL (natural log scale).

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

For each cohort, with a total of 50 subjects from Parts A and B combined, the chance to observe at least 1 SAE is 92%, assuming the SAE incidence rate is 5% (observed in GS-US-292-0102). After amendment 2 of the study protocol was finalized, the adult data included in E/C/F/TAF (Genvoya®) label have become available and will be used as historical control for comparison for Cohort 2 (ie, intensive PK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK 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 was 23, a total of 23 subjects would provide 90% power for EVG AUC_{tau} and 88% power for TAF AUC_{last} to conclude exposure equivalence between

children and adults, assuming the expected geometric mean ratios was 1, equivalency boundary was 70% to 143%, two one-sided tests were each performed at an alpha level of 0.05, and the intersubject standard deviation (natural log scale) of EVG AUC_{tau} and TAF AUC_{last} was 0.34 ng•hr/mL and 0.52 ng•hr/mL, respectively.

A total of 23 subjects from Cohort 2 Part A would also provide 86% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of clearance and volume of distribution of TAF respectively, assuming a CV of 53% for clearance and 76% for volume of distribution (based on population PK data from GS US-292-0104 and GS-US-292-0111 combined).

Cohort 3

Twenty-five evaluable subjects 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 ratios is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level of 0.05, and the intersubject standard deviations (natural log scale) of EVG AUC_{tau} and TAF AUC_{tau} are 0.34 ng•hr/mL and 0.52 ng•hr/mL. For historical adult data, we used intensive PK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK data from Studies GS-US-292-0104 and GS-US-292-0111 combined for TAF AUC_{tau}.

Twenty-five evaluable subjects will also provide > 99% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of apparent clearance and volume of distribution of TAF respectively, assuming the standard deviation natural log scale is 0.51 for CL and 0.54 for V_z (based on population PK data from Studies GS-US-292-0104 and GS-US-292-0111 combined).

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell 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
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CFR	Code of Federal Regulations
CL_{cr}	creatinine clearance
C_{max}	maximum observed serum/plasma/peripheral blood mononuclear concentration of drug
C_{last}	last observed quantifiable concentration of the drug in plasma
CNS	central nervous system
COBI	cobicistat (GS-9350)
CPK	creatine phosphokinase
CRF	case report form
CRO	contract (or clinical) research organization
C_{tau}	observed drug concentration at the end of the dosing interval
CTX	C-telopeptide
CV	coefficient of variation
CYP	cytochrome P450
DAVG	average area under the dosing interval
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DRV	darunavir

DXA	dual energy x-ray absorptiometry
E/C/F/TDF	single tablet regimen of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EFV	efavirenz, Sustiva®
EFV/FTC/TDF	single tablet regimen of efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, Atripla®
EU	European Union
EVG	elvitegravir (GS-9137)
EVG/COBI/FTC/TAF, E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
FDA	Food and Drug Administration
FTC	emtricitabine, Emtriva®
FTC/RPV/TDF	emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg, Complera® FTC/TDF
GCP	Good Clinical Practice (Guidelines)
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
GLPS	Global Patient Safety
GSI	Gilead Sciences, Inc.
GS-9137	elvitegravir, EVG, 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid
GS-9350	cobicistat, COBI, 1,3-Thiazol-5-ylmethyl (2R,5R)-(5-(((2S)-2-((methyl((2-(propan-2-yl)-1,3-thiazol-4-yl(methyl(carbamoyl)amino((-4-(morpholin-4-yl)butanamido
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMG-CoA	5-hydroxy-3-methylglutaryl-coenzyme A
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ID	identification
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
Ig	immunoglobulin

IND	investigational new drug
INH	isonicotinylhydrazine, Isoniazid (Laniazid, Nydrazid)
INSTI	integrase strand transfer inhibitor
IRB	institutional review board
ITT	intent to treat (analysis or subset)
IV	intravenous
KS	Kaposi's sarcoma
LD	low dose
LDL	low-density lipoprotein
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OTC	over the counter
PAH	pulmonary arterial hypertension
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PI/r	ritonavir boosted-protease inhibitor
PK	pharmacokinetic
PR	pulse rate
PT	preferred term (in Section 8)
PT	prothrombin time (in Appendix 4)
PTH	parathyroid hormone
QTc	corrected QT
RAL	raltegravir
RBP	retinol-binding protein
REB	Research Ethics Board
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir, Norvir®
SAE	serious adverse event
S_{cr}	serum creatinine
SOC	System Organ Class
SOP	standard operating procedure
Spo4	serum phosphate concentration

STR	Single Tablet Regimen
SUSAR	suspected unexpected serious adverse reaction
SVR	suboptimal virologic response
$T_{½}$	half life
TAF	tenofovir alafenamide (GS-7340)
TBLH	total body less head
TDF	tenofovir disoproxil fumarate, Viread®
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TLOVR	time to loss of virologic response
t_{max}	time (observed time point) of C_{max}
TPV/r	ritonavir-boosted tipranavir
UACR	Urine Albumin to Creatinine Ratio
ULN	upper limit of the normal range
UPCR	Urine Protein to Creatinine Ratio
US	United States
Upo4	urine phosphate concentration
VR	virologic rebound

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.1 million people in North America and Western and Central Europe living with HIV-1 and 36.7 million people worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}, including 2.1 million children under 15 years of age {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. This figure is likely to underestimate the HIV disease burden in the pediatric population using the European Medicines Agency (EMA) categorization of adolescence as from 12 to 16 or 18 years, depending on the region (EMA, Note for Guidance CPMP/ICH/2711/99). The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {Mocroft 1998, Palella 1998, Sterne 2005}.

Disease Pathophysiology

The pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ARV therapy are similar between HIV-1 infected adult and pediatric patients. However, there are some important and unique issues for HIV-1 infected infants, children, and adolescents, including the following {Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children 2011}:

- Acquisition of infection through perinatal exposure for many infected children
- In utero, intrapartum, and/or postpartum neonatal exposure to zidovudine and other ARV medications in most perinatally infected children
- Age-specific differences in CD4+ cell counts and percentages
- Changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance
- Differences in the clinical and virologic manifestations of perinatal HIV-1 infection secondary to the occurrence of primary infection in growing, immunologically immature persons
- Special considerations associated with adherence to ARV treatment for infants, children, and adolescents

- Need for longer duration of therapy, with potentially greater implications than in adults for long-term toxicity and development of resistance

- Differences in physiological development of certain body systems, including the skeletal system, where peak bone mass is not achieved until early adulthood

Treatment

The goal of ARV therapy for HIV-1 infection is to delay disease progression, improve immune function, and increase the duration of survival by achieving maximal and prolonged suppression of HIV-1 replication. The availability of highly active antiretroviral therapy (HAART) combinations for the treatment of HIV-1 infection has resulted in a dramatic reduction in Acquired Immunodeficiency Syndrome (AIDS) related morbidity and mortality in the US and Europe {Mocroft 1998, Palella 1998, Sterne 2005}. However, eradication of the virus is not possible with therapies that are currently available. These therapies have several distinct adverse events such as mitochondrial dysfunction, metabolic abnormalities, hematologic toxicities, and allergic reactions.

The 2018 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection generally recommend the use of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a 3rd agent (a non-nucleoside reverse transcriptase inhibitor [NNRTI], a boosted protease inhibitor [PI] or an integrase strand transfer inhibitor [INSTI]) for treatment of children and adolescents with HIV infection depending on age and sexual maturity rating for adolescents (DHHS guidelines May 2018). The choice of a regimen, including the 3rd agent, is individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics and results of resistance testing {Department of Health and Human Services (DHHS) 2018}.

Studies have shown that a once-daily STR significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {Airoldi 2010, Bangsberg 2010, Dejesus 2009, Hodder 2010, Sax 2015}. Due to a longer duration of high adherence, patients taking STRs also have better clinical outcomes, such as fewer hospitalizations, compared with multiple-tablet regimens {Sax 2010}. The following STRs are currently approved for once-daily administration in the treatment of HIV-1 infection in adolescents and/or children: EFV/FTC/TDF (Atripla®), FTC/RPV/TDF (Complera®/Eviplera®), EVG/COBI/FTC/TDF (Stribild®), EVG/COBI/FTC/TAF (Genvoya®), BIC/FTC/TAF (Biktarvy®), R/F/TAF (Odefsey®) and Triumeq®.

Tenofovir disoproxil fumarate (TDF) is a preferred NRTI among recommended regimens for treatment-naive HIV-infected adults and adolescents, but is associated with nephrotoxicity and reduced bone mineral density {Panel on Antiretroviral Guidelines for Adults and Adolescents 2012}. Lifelong antiretroviral treatment and the increasing comorbidities being recognized and treated in HIV-infected patients creates an urgent need to improve the safety profile of regimens that most effectively suppress HIV replication.

Tenofovir alafenamide (TAF, also known as GS-7340) is an oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Gilead has coformulated TAF with the integrase strand transfer inhibitor EVG, cobicistat (COBI, GS-9350), and FTC into a STR. Compared to TDF, the use of TAF in the E/C/F/TAF STR provides enhanced lymphatic delivery of TFV, resulting in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate (TFV-DP), and lower systemic circulating levels of TFV. These features are hypothesized to translate into more effective suppression of viral replication, and an improved tolerability and safety profile. FTC/TAF (Descovy), Genvoya, R/F/TAF (Odefsey), and GS-9883/Emtricitabine/Tenofovir Alafenamide (Biktarvy) are all FDC's containing TAF that have been approved in adolescents (US and EU) and children 6 to <12 years of age weighing ≥ 25 kg (Genvoya in the US and EU and Descovy in the US only).

EVG can be dosed once daily when used with a pharmacoenhancing (boosting) agent like ritonavir 100 mg or COBI. COBI is devoid of anti-HIV activity, may have less adverse biochemical effects (e.g., effect on adipocyte functions such as lipid accumulation) relative to ritonavir, and can be coformulated as a tablet with other ARV agents that require boosting. Gilead Sciences has coformulated a single tablet regimen of COBI with EVG, FTC and TAF. This STR may be an attractive option for adolescents and children with HIV-1 infection.

This study represents the first use of the E/C/F/TAF STR in adolescents and children 6 to < 12 years of age. E/C/F/TAF was approved in adults and pediatric patients 12 years of age and older in the US and EU in 2016 and most recently for 6 to < 12 year olds and weighing ≥ 25 kg. Please refer to the E/C/F/TAF local labeling and the Investigator's Brochure for contraindications, warnings and precautions, and interactions.

1.1.1. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF)

A brief summary of the clinical trials of E/C/F/TAF STR for the treatment of HIV-1 infection are below. Please refer to the E/C/F/TAF Investigator's Brochure for additional details:

The efficacy and safety of E/C/F/TAF (Genvoya) in HIV-1 infected, treatment-naïve adults are based on 144-week data from two randomized, double-blind, active-controlled studies, GS-US-292-0104 ("Study 104") and GS-US-292-0111 ("Study 111") (N=1733).

The efficacy and safety of Genvoya in virologically-suppressed HIV-1 infected adults are based on 96-week data from a randomized, open-label, active-controlled study, GS-US-292-0109 ("Study 109") (N=1436).

The efficacy and safety of Genvoya in HIV-1 infected, virologically-suppressed patients with mild to moderate renal impairment is based on 144-week data from an open-label study, GS-US-292-0112 ("Study 112") (N = 242).

The efficacy and safety of Genvoya in HIV-1 infected pediatric patients are based on 48-week data in treatment-naïve patients between the ages of 12 to < 18 years (weighing ≥ 35 kg) (N=50) and 24-week data in virologically suppressed patients between the ages of 6 to < 12 years (weighing ≥ 25 kg) (N = 23) from Cohorts 1 and 2, respectively, of this study (GS-US-292-0106).

Treatment-Naïve Patients

In both Study 104 and Study 111, patients were randomized in a 1:1 ratio to receive either Genvoya (N = 866) once daily or Stribild (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; N = 867) once daily.

In Studies 104 and 111, the mean age was 36 years (range 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range 1.3-7.0). The mean baseline CD4+ cell count was 427 cells/mm^3 (range 0-1360) and 13% had CD4+ cell counts less than 200 cells/mm^3. Twenty-three percent of patients had baseline viral loads greater than 100,000 copies/mL.

In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies/mL to less than or equal to 400,000 copies/mL, or greater than 400,000 copies/mL), by CD4 count (less than 50 cells/μL, 50-199 cells/μL, or greater than or equal to 200 cells/μL), and by region (US or ex-US).

Treatment outcomes of Studies 104 and 111 through 48 and 144 weeks are presented in Table 1-1.

Table 1-1. Pooled Virologic Outcomes of Studies 104 and 111 at Weeks 48[a] and 144[b]

	Week 48		Week 144	
	Genvoya (N = 866)	**Stribild (N = 867)**	**Genvoya (N = 866)**	**Stribild (N = 867)**
HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment Difference	2.0% (95% CI = −0.7% to 4.7%)		4.2% (95% CI = 0.6% to 7.8%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No Virologic Data at Week 48 or 144 Window	4%	6%	11%	16%
Discontinued Study Drug Due to AE or Death[d]	1%	2%	1%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[e]	2%	4%	9%	11%
Missing Data During Window but on Study Drug	1%	<1%	1%	1%

	Week 48		Week 144	
	Genvoya (N = 866)	**Stribild (N = 867)**	**Genvoya (N = 866)**	**Stribild (N = 867)**
Proportion (%) of Patients with HIV-1 RNA <50 copies/mL by Subgroup				
Age < 50 years ≥ 50 years	716/777 (92%) 84/89 (94%)	680/753 (90%) 104/114 (91%)	647/777 (83%) 82/89 (92%)	602/753 (80%) 92/114 (81%)
Sex Male Female	674/733 (92%) 126/133 (95%)	673/740 (91%) 111/127 (87%)	616/733 (84%) 113/133 (85%)	603/740 (81%) 91/127 (72%)
Race Black Nonblack	197/223 (88%) 603/643 (94%)	177/213 (83%) 607/654 (93%)	168/223 (75%) 561/643 (87%)	152/213 (71%) 542/654 (83%)
Baseline Viral Load ≤ 100,000 copies/mL 100,000 copies/mL	629/670 (94%) 171/196 (87%)	610/672 (91%) 174/195 (89%)	567/670 (85%) 162/196 (83%)	537/672 (80%) 157/195 (81%)
Baseline CD4+ cell count < 200 cells/mm^3 ≥ 200 cells/mm^3	96/112 (86%) 703/753 (93%)	104/117 (89%) 680/750 (91%)	93/112 (83%) 635/753 (84%)	94/117 (80%) 600/750 (80%)

a Week 48 window was between Day 294 and 377 (inclusive).
b Week 144 window was between Day 966 and 1049 (inclusive).
c Includes patients who had ≥ 50 copies/mL in the Week 48 or 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

At Week 144, Genvoya demonstrated statistical superiority (P = 0.021) in achieving HIV-1 RNA < 50 copies/mL when compared to Stribild.

In Studies 104 and 111, the mean increase from baseline in CD4+ cell count at Week 144 was 326 cells/mm^3 in Genvoya-treated patients and 305 cells/mm^3 in Stribild-treated patients (P = 0.06).

Bone Mineral Density: In a pooled analysis of Studies 104 and 111, the effects of Genvoya compared to that of Stribild on bone mineral density (BMD) change from baseline to Week 144 were assessed by dual-energy X-ray absorptiometry (DXA). As shown in Table 1-2, in patients who had both baseline and Week 144 measurements (N = 690 and 702 in the Genvoya group and N = 683 and 686 in the STRIBLD group, for hip and spine, respectively) there were smaller decreases in BMD in the Genvoya group as compared to Stribild.

Table 1-2. Measures of Bone Mineral Density in Studies 104 and 111 (Week 144 Analysis)

	Genvoya	Stribild	Treatment Difference
Hip DXA Analysis	N = 690	N = 683	
Mean Percent Change in BMD	−0.8%	−3.4%	2.6% P < 0.001
Patients with Categorical Change: 3% Decrease in BMD 3% Increase in BMD	28% 13%	55% 6%	--
Patients with No Decrease (≥ zero % change) in BMD	40%	19%	--
Lumbar Spine DXA Analysis	N=702	N=686	
Mean Percent Change in BMD	−0.9%	−3.0%	2.0% P < 0.001
Patients with Categorical Change: 3% Decrease in BMD 3% Increase in BMD	30% 13%	49% 7%	--
Patients with No Decrease (≥ zero % change) in BMD	39%	22%	--

Changes in Renal Laboratory Tests: Laboratory tests were performed in Studies 104 and 111 to compare the effect of TAF, administered as a component of Genvoya, to that of TDF, administered as a component of Stribild, on renal laboratory parameters. As shown in Table 1-3, statistically significant differences were observed between treatment groups that favored Genvoya. In these studies, there were statistically significant differences between treatment groups for increases in serum creatinine and changes in proteinuria, including Urine Protein to Creatinine Ratio (UPCR), Urine Albumin to Creatinine Ratio (UACR), urine retinol-binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio that favored Genvoya.

Table 1-3. Change from Baseline in Renal Laboratory Tests in Studies 104 and 111 (Week 144 analysis)

	Genvoya N = 866	Stribild N = 867	Treatment Difference
Serum Creatinine (mg/dL)[a]	0.04 ± 0.12	0.07 ± 0.13	−0.04 P < 0.001
Proteinuria by Urine Dipstick[b]	40%	45%	P = 0.027
Urine Protein to Creatinine Ratio [UPCR][c]	−10.5%	25.2%	P < 0.001
Urine Albumin to Creatinine Ratio [UACR][c,d]	−5.2%	5.2%	P < 0.001
Urine RBP to Creatinine Ratio[c]	34.8%	111%	P < 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio[c]	−25.7%	53.8%	P < 0.001

a Mean change ± standard deviation
b Includes all severity grades (1-3).
c Median percent change.
d Week 96 analysis.

Virologically Suppressed Patients

In Study 109, the efficacy and safety of switching from either ATRIPLA, TRUVADA plus atazanavir (boosted by either cobicistat or ritonavir), or Stribild to Genvoya were evaluated in a randomized, open-label study of virologically-suppressed (HIV-1 RNA < 50 copies/mL) HIV-1 infected adults (N = 1436). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had no resistance mutations to any of the components of Genvoya prior to study entry. Patients were randomized in a 2:1 ratio to either switch to Genvoya at baseline (N = 959), or stay on their baseline antiretroviral regimen (N = 477). Patients had a mean age of 41 years (range 1-77), 89% were male, 67% were White, and 19% were Black. The mean baseline CD4+ cell count was 697 cells/mm^3 (range 79-1951)

Patients were stratified by prior treatment regimen. At screening, 42% of patients were receiving TRUVADA plus atazanavir (boosted by either cobicistat or ritonavir), 32% of patients were receiving Stribild, and 26% of patients were receiving ATRIPLA.

Pediatric Patients

In this study (GS-US-292-0106), the efficacy, safety, and pharmacokinetics of Genvoya in HIV-1-infected patients were evaluated in open-label studies in treatment-naïve patients between the ages of 12 to < 18 years (weighing ≥ 35 kg) (N = 50), in virologically suppressed patients between the ages of 6 to < 12 years (weighing ≥ 25 kg) (N = 52), and in virologically suppressed patients at least 2 years of age (weighing at least 14 to < 25 kg) (N = 27).

Cohort 1: Treatment-naïve adolescents (12 to < 18 years; weighing ≥ 35 kg), Week 48 Analysis

Patients in Cohort 1 had a mean age of 15 years (range: 12 to 17), 44% were male, 12% were Asian, and 88% were black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95 to 1110), and median CD4% was 23% (range: 7% to 45%). 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL.

Among the patients in Cohort 1 treated with Genvoya, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL at Week 48. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. Three of 50 patients had virologic failure at Week 48; no emergent resistance to Genvoya was detected through Week 48.

Among the patients in Cohort 1 who had both baseline and Week 48 measurements (N=47 and 44 for the lumbar spine and total body less head [TBLH], respectively), mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for TBLH.

Cohort 2: Virologically suppressed children (6 to < 12 years; weighing ≥ 25 kg), Week 48 Analysis

Patients in Cohort 2 had a mean age of 10 years (range: 7 to 11), a mean baseline weight of 32 kg (range: 26 to 58), 42% were male, 25% were Asian, and 71% were black. At baseline, median CD4+ cell count was 926 cells/mm^3 (range: 336 to 1611) and median CD4% was 38% (range: 23% to 51%).

After switching to Genvoya, 98% (51/52) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count was -66 cells/mm^3 and the mean change in CD4% was -0.6% at Week 48. One of 52 patients met the criteria for inclusion in the resistance analysis population through Week 48; no emergent resistance to Genvoya was detected through Week 48.

Among the patients in Cohort 2 who had both baseline and Week 48 measurements (N=49 and 51, for lumbar spine and TBLH, respectively), mean BMD increased from baseline to Week 48, +3.9% at the lumbar spine and +4.2% for TBLH.

Cohort 3: Virologically suppressed children (≥ 2 years; weighing 14 to < 25 kg), Week 48 Analysis

Patients in Cohort 3 had a mean age of 6 years (range: 3 to 9), a mean baseline weight of 19 kg (range: 15 to 24), 37% were male, 11% were Asian, and 89% were black. At baseline, median CD4+ cell count was 1061 cells/mm^3 (range: 383 to 2401) and median CD4% was 37% (range: 24% to 53%).

After switching to Genvoya, 96.3% (26 of 27) of patients in Cohort 3 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count was -179 cells/mm^3 and the mean change in CD4% was 0.2% at Week 48. One of 27 patients (3.7%) qualified for viral resistance testing at Week 48; no resistance to study drug was detected and the patient resuppressed HIV-1 RNA to < 50 copies/mL while remaining on study drug.

Among the patients in Cohort 3, mean BMD increased from baseline to Week 48, +5.3% at the lumbar spine and +7.2% for TBLH.

For further information, including the results of studies of Genvoya in adults and adolescents, please refer to the current Genvoya Investigator's Brochure.

1.2. Rationale for the Current Study

The success of HAART and the apparent benefits of maximally suppressed viremia has shifted clinical attention towards antiretroviral agents that optimize long-term safety and tolerability. Young, newly infected patients are diagnosed earlier, initiate therapy earlier, and look ahead towards lifelong therapy, often greater than fifty years {Prejean 2011}. Renal and bone health, in both of these contexts, are increasingly important {Capeau 2011}.

Based on the data from this study and extrapolation to adult efficacy and safety data, Genvoya was approved in adults and pediatric patients 12 years of age and older in the US and EU in 2016 and approved in 2017 for use in pediatric patients 6 to < 12 year of age weighing ≥ 25 kg.

HIV-infected children ages ≥ 2 years of age will benefit from the availability of an age-appropriate formulation containing TAF, which has the potential for an improved renal and bone safety profile relative to TDF, an important consideration for a population in which peak bone mass has not yet been achieved and for whom HIV treatment is anticipated to be life-long.

The objective of this study is to characterize the pharmacokinetics (PK), and confirm the dose of E/C/F/TAF and to evaluate the safety, tolerability and antiviral activity of E/C/F/TAF as an STR in treatment-naive HIV-1 infected adolescents 12 to less than 18 years of age and in virologically suppressed HIV-1 infected children 2 to < 12 years of age.

1.3. Rationale for Dose Selection

The proposed E/C/F/TAF doses for this study are expected to provide plasma exposures in the pediatric population that are comparable to those associated with safety and efficacy in adults.

E/C/F/TAF Dose in Adolescents 12 to < 18 years old, weighing ≥ 35 kg

The FDA-approved dose of E/C/F/TAF in adolescents 12 to < 18 years and weighing ≥ 35 kg is the adult strength STR (150/150/200/10 mg).

E/C/F/TAF Dose in Children ≥ 2 years old weighing ≥ 25 kg, and weighing ≥ 14 to < 25 kg

The FDA-approved dose of E/C/F/TAF in children weighing ≥ 25 kg is the adult strength STR (150/150/200/10 mg). For children weighing ≥ 14 to < 25 kg, a low dose E/C/F/TAF (E/C/F/TAF LD) tablet of 90/90/120/6 mg is proposed for evaluation. The observed exposures following administration of E/C/F/TAF 150/150/200/10 mg in children weighing ≥ 25 kg or predicted exposures of E/C/F/TAF 90/90/120/6 mg in children weighing ≥ 14 to < 25 kg are comparable to those observed in adults for all analytes (EVG, COBI, FTC, TAF and TAF-metabolite TFV). The dosing nomogram is structured to avoid subtherapeutic dosing in a population requiring lifelong therapy from a young age, in which the implications of virologic failure may be greater than in adults.

Rationale for E/C/F/TAF Dose in Children weighing ≥ 25 kg

EVG:

EVG is differentially dosed in adults in order to achieve comparable EVG exposures depending on the co-administered regimen: 85 mg with LPV/r or ATV/r; EVG 150 mg with COBI and other boosted PIs.

Preliminary data are available in treatment-experienced children 6 to < 12 years old on a regimen containing LPV/r or ATV/r from Study GS-US-183-0160. Of 14 participants who completed the PK substudy, 6 were taking the adult strength EVG 85 mg (body weight ≥ 30 kg) and 8 were taking a reduced strength EVG 50 mg (body weight 17 to < 30 kg). Plasma exposures of EVG were similar to those previously observed in adolescents, and higher than in adults (GMR AUC 1.36; GMR C_{trough} 1.29) with all participants having an EVG C_{trough} above the protein-binding adjusted IC_{95} of 44.5 ng/mL. Plasma exposures support using the adult EVG dose in 6 to < 12 years olds weighing ≥ 30 kg. Simulation for children with a body weight between 25 and < 30 kg demonstrated that when combined with LPV/r, administration of the higher dose (85 mg) would result in slightly higher, but acceptable EVG exposures. EVG was well-tolerated in this study, with no related SAEs or AEs leading to EVG discontinuation (with one related AE of mild dizziness). Therefore, the adult 150 mg dose of EVG is proposed for use in children 6 to < 12 years old weighing ≥ 25 kg.

COBI:

The 150 mg dose of COBI is the adult dose, selected for its efficacy in boosting EVG exposures. COBI dose selection was guided by dose/data available for ritonavir boosting in various pediatric weight bands and similarities in observed dose-dependent pharmacodynamic effects (CYP3A inhibition) for COBI versus ritonavir (RTV) in adults. Comparison of RTV and COBI dose-ranging PK and pharmacodynamic (Studies GS-US-183-0113, GS-US-216-0101, GS-US-216-0110, and GS-US-236-0101) indicate comparable CYP inhibition/boosting of probe/other substrates, including ARVs. The proposed COBI doses generally represent a higher dose on a mg/kg basis relative to the adult dose, and are expected to provide sufficient boosting activity within the context of E/C/F/TAF STR. The adult 150 mg dose of COBI is proposed for administration to pediatric subjects weighing ≥ 25 kg.

FTC:

Emtricitabine is approved to be dosed at ≤ 6.1 mg/kg in children with either a capsule or oral solution formulation {EMTRIVA® 2012}. Per the current Emtriva label, the approved dose of 200 mg FTC can be administered in adults with normal renal function and those with mild renal impairment (50-80 mL/min), in whom FTC exposures were shown to be approximately 70% higher than adults with normal renal function {EMTRIVA® 2012}. In addition, a proposal for FTC/TDF low-dose tablets from the WHO Paediatric Antiretroviral Working Group {World Health Organization (WHO) 2011} allows FTC doses up to 8.57 mg/kg (corresponding to a 40% increase in dose over 6.1 mg/kg) for use in children. Given the approved doses for FTC and its dose-proportional pharmacokinetics, a modest increase of FTC dose in children is expected to result in exposures in the range of those providing a favorable risk:benefit profile. The E/C/F/TAF (150/150/200/10 mg) adult-strength STR for use in patients 6 to < 12 years of age weighing ≥ 25 kg provides a range of FTC doses comparable to the approved doses, and does not exceed 8.57 mg/kg.

TAF:

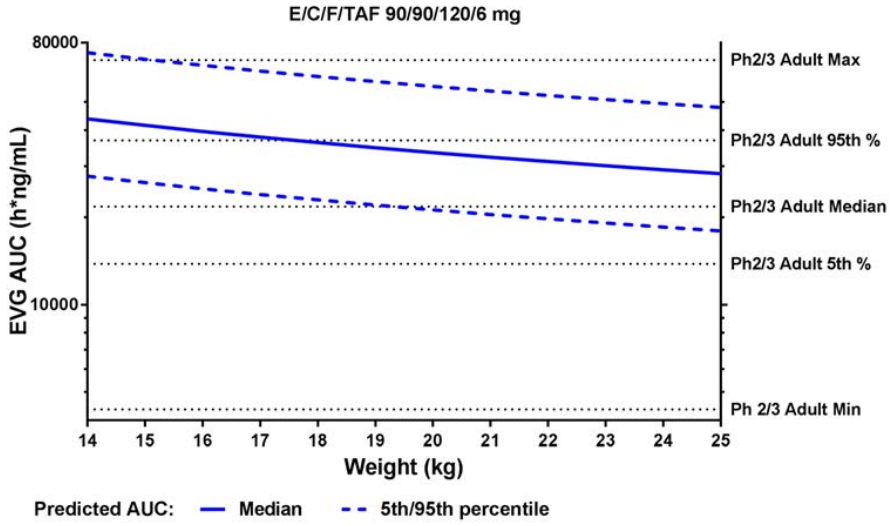
The TAF dose selection in children 6 to < 12 years of age is based on the established TDF dose to exposure relationship in children and adults, where it has been shown that administration of TDF doses at approximately twice the average adult dose (on a mg/kg basis) result in TFV exposures in children within the range observed in adults {Gilead Sciences Inc 2012}.

The TAF dose proposed for a 75 kg adult is 0.13 mg/kg when used with boosted regimens such as E/C/F/TAF STR. For a subject weighing ≥ 25 kg to < 35 kg, administration of TAF 10 mg (in the context of E/C/F/TAF STR) corresponds to a range of TAF dose per body weight of 0.29 to 0.40 mg/kg (approximately 2 to 3 times the adult dose). This is predicted to result in TAF exposures in children within the range observed in adults and to yield maximum exposures in the lowest weight ranges of each band less than 2-fold above mean TAF exposure in adults.

Rationale for E/C/F/TAF Dose in Children weighing ≥ 14 to < 25 kg

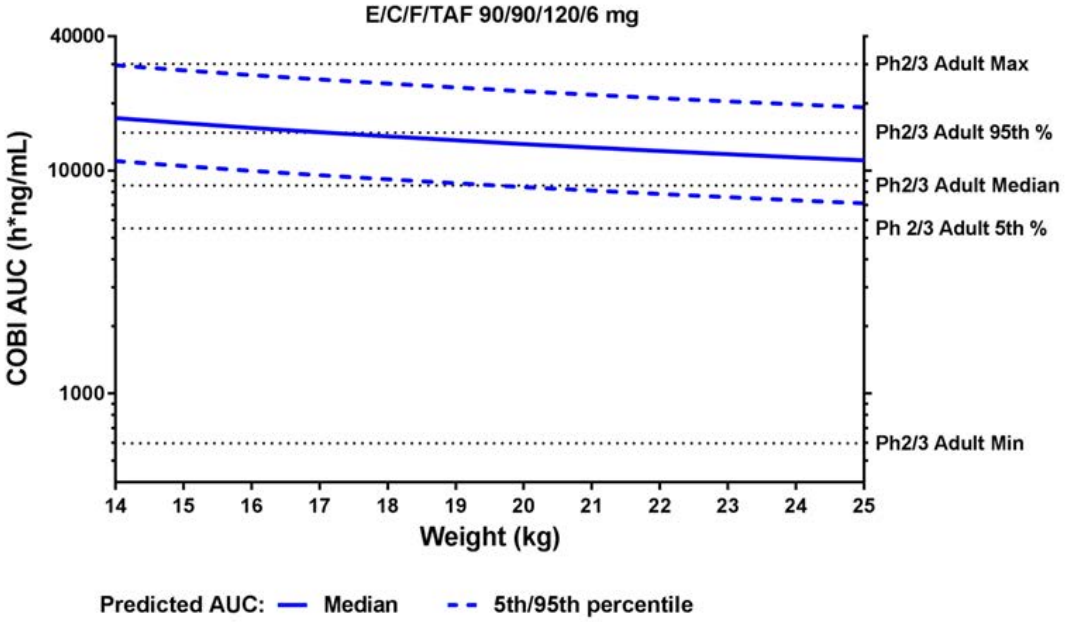
For dose selection in children weighing ≥ 14 to < 25 kg, EVG, COBI, FTC, TAF and TFV exposures were predicted by allometric scaling of adult exposures considering correlations between body weight and clearance (CL) capacity. Model-predicted systemic exposures of EVG, COBI, FTC, TAF and TFV in children weighing ≥ 14 to < 25 kg administered the E/C/F/TAF LD STR (90/90/120/6 mg) are presented in Figure 1-1, Figure 1-2, Figure 1-3, Figure 1-4 and Figure 1-5, respectively. These simulations indicate that the predicted exposure ranges of EVG, COBI, FTC, TAF and TFV in children 2 to < 12 years weighing ≥ 14 to < 25 kg following administration of E/C/F/TAF 90/90/120/6 mg are comparable to those observed in the adult Phase 2/3 population, and in children 6 to < 12 years weighing ≥ 25 kg who received the adult strength STR.

Figure 1-1. Predicted EVG AUC in Children Following Administration of E/C/F/TAF 90/90/120/6 mg



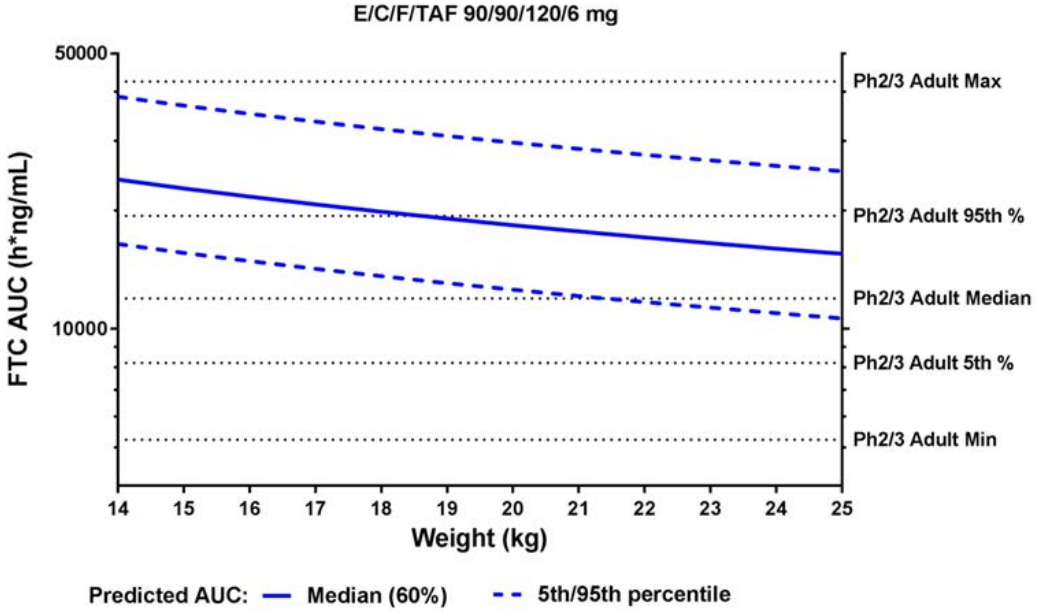
The adult exposures for EVG were the population PK predicted exposures from the STB Phase 2/3 program (Stribild NDA 203100 SN 0000, m5.3.3.5, COBI-boosted EVG Population PK report)

Figure 1-2. Predicted COBI AUC in Children Following Administration of E/C/F/TAF 90/90/120/6 mg



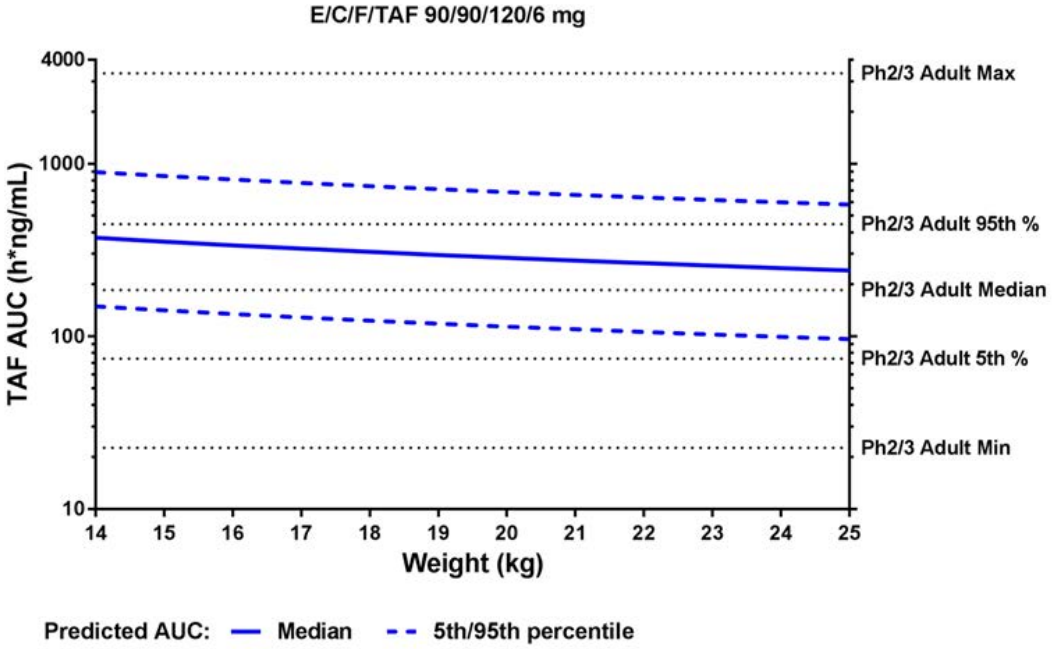
The adult exposures for COBI were the population PK predicted exposures from Phase 2/3 studies with Stribild (STB) or ATV/co + Truvada (ATV/co + TVD) (Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, GS-US-216-0105, and GS-US-216-0114)

Figure 1-3. Predicted FTC AUC in Children Following Administration of E/C/F/TAF 90/90/120/6 mg



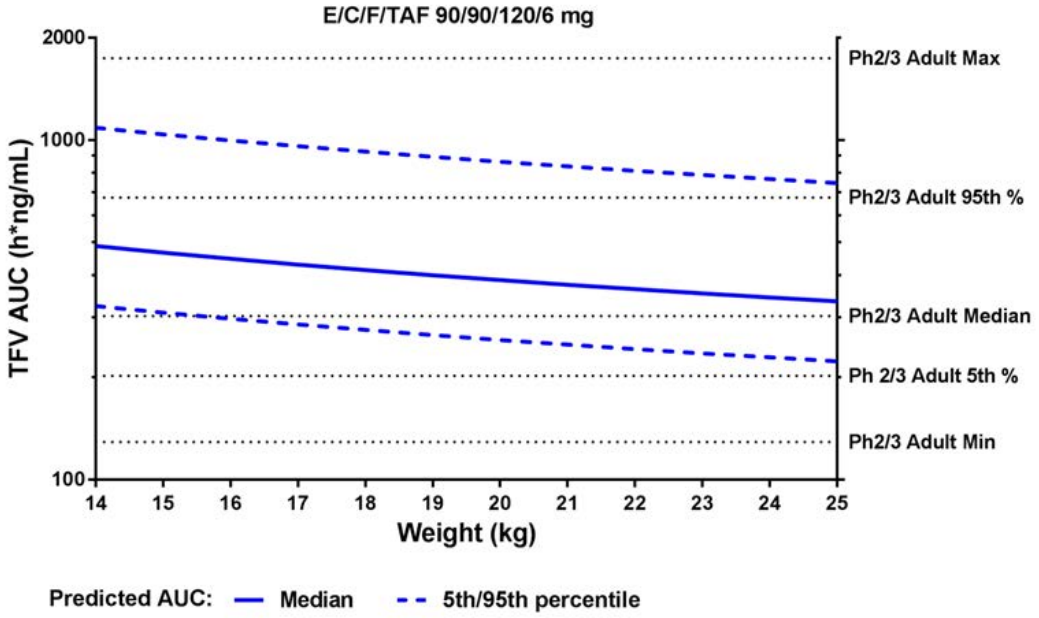
The adult exposures for FTC were the exposures from Phase 2/3 studies with STB (Studies GS-US-236-0101, GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, and GS-US-236-0110)

Figure 1-4. Predicted TAF AUC in Children Following Administration of E/C/F/TAF 90/90/120/6 mg



The adult exposures for TAF were the population PK predicted exposures from the GEN Phase 2/3 program (Genvoya NDA 207561, m5.3.3.5, Population PK Analysis of TAF and TFV following Administration of E/C/F/TAF STR)

Figure 1-5. Predicted TFV AUC in Children Following Administration of E/C/F/TAF 90/90/120/6 mg



The adult exposures for TFV were the population PK predicted exposures from the GEN Phase 2/3 program (Genvoya NDA 207561, m5.3.3.5, Population PK Analysis of TAF and TFV following Administration of E/C/F/TAF STR)

2. OBJECTIVES

Cohort 1

The primary objectives of this study 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 for this study 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

Cohort 2

The primary objectives of this study 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 HIV-1 infected children 6 to < 12 years of age

The secondary objectives for this study 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

Cohort 3

The primary objectives of this study 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 LD 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 of this study 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

CCI [redacted]

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- CCI [redacted]

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This protocol describes an open-label, multicenter, multi-cohort, single-arm study of the pharmacokinetics (PK), safety, tolerability, and antiviral activity of the E/C/F/TAF STR in HIV-1 infected ARV treatment-naive adolescents and virologically suppressed children.

A total of 50 adolescents (12 to < 18 years of age) and up to 75 children (6 to < 12 years of age) of either sex will be enrolled to receive the STR of E/C/F/TAF once daily with food as follows:

Part A

Intensive PK samples will be analyzed for Cohorts 1 and 2 once they are available from 18 subjects regardless of age distribution and for all Cohort 3 subjects.

Cohort 1, Part A: EVG, TAF and COBI exposures will be compared to historical data from adult HIV-1 infected subjects. TAF data will also be compared to HIV-negative subjects from 292-0103 study. FTC and TFV exposures will be compared to historical data in HIV-infected adults and available data in adolescent subjects. Cohort 2, Part A: EVG, TAF, COBI, FTC and TFV exposures will be compared to historical adult data.

EVG and TAF dose confirmation will be established if the 90% confidence intervals of geometric mean ratios for AUC in adolescents and children (respectively) versus those in adults are within the equivalency bounds of 70-143%.

Following completion of the Intensive PK visit, subjects will continue to receive E/C/F/TAF STR and return for scheduled study visits through Week 48.

Cohort 1 (Adolescents 12 to < 18 years of age)

- Eighteen to 24 eligible subjects will be initially enrolled to evaluate the steady state PK, and confirm the dose of the E/C/F/TAF STR.
- Part A will aim to enroll at least 6 subjects 12 to < 15 years of age and at least 6 subjects 15 to < 18 years of age.
- If at least 6 subjects ages 12 to < 15 years and 6 subjects ages 15 to < 18 have not been enrolled at the time of the Intensive PK analysis, Part A enrollment will remain open in order to enroll sufficient subjects to meet the minimum enrollment of the 2 age subgroups.
- Subjects enrolled in Part A will participate in an Intensive PK evaluation on Week 4. Samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing), 5 minutes, 0.25, 0.5, 1, 1.5, 2, 4, 5, 8 and 24 hours post-dose.

Cohort 2 (Children 6 to < 12 years of age and weighing ≥ 25 kg)

- Eighteen to 24 eligible subjects will be enrolled to evaluate the EVG and TAF plasma PK and confirm the dose of EVG and TAF.
- Subjects will participate in an Intensive PK evaluation on Week 4.

Cohort 3 (Children ≥ 2 years of age and weighing ≥ 14 to < 25 kg)

- Up to 25 eligible subjects will be enrolled to evaluate the EVG and TAF plasma PK and confirm the dose of EVG and TAF.
- Subjects will participate in an Intensive PK evaluation on Week 2.

Part B

Cohort 1

Screening will be initiated into Cohort 1, Part B following confirmation of EVG and TAF exposure in at least 18 subjects from Cohort 1, Part A. The additional 26 to 32 subjects will be enrolled in Cohort 1, Part B to evaluate the safety, tolerability and antiviral activity of the E/C/F/TAF STR in at least 50 patients, including all subjects enrolled in Cohort 1 (Parts A and Part B combined).

Cohort 2

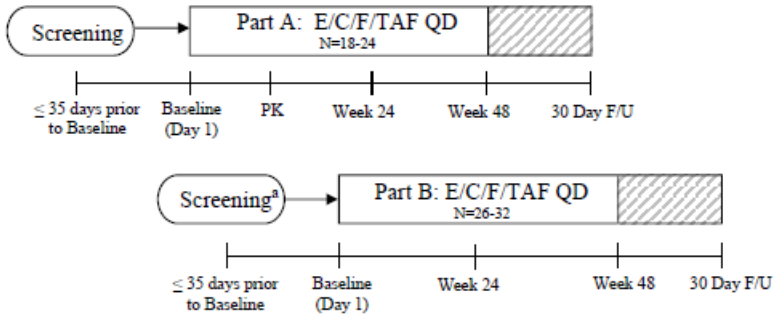
Screening will be initiated in subjects 6 to < 12 years of age into Cohort 2, Part B based on exposure data from at least 18 subjects from Cohort 2, Part A. The additional 26 to 32 subjects will be enrolled in Cohort 2, Part B to evaluate the safety, tolerability and antiviral activity of the E/C/F/TAF STR in at least 50 patients, including all subjects enrolled in Cohort 2 (Parts A and B combined).

Cohort 3

No Part B for this cohort. All subjects will be enrolled in Part A and will complete an Intensive PK evaluation.

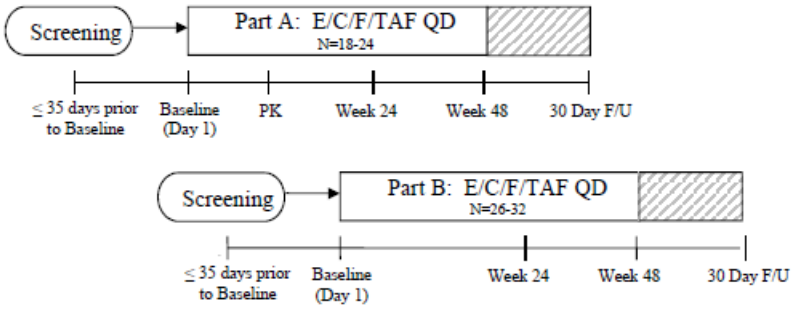
Figure 3-1. Study Schema

Cohort 1:

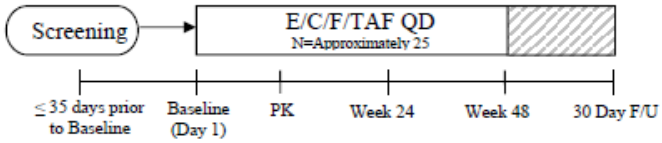


a Screening for Part B will commence after the PK data from Part A confirms the adolescent dose of the E/C/F/TAF STR

Cohort 2:



Cohort 3:



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of 50 adolescents (12 to < 18 years of age) and up to 75 children (2 to < 12 years of age) who meet the eligibility criteria will be enrolled into this study.

Replacement subjects may be enrolled if subjects do not complete all Intensive PK procedures or if PK data are incomplete. Replacement subjects will not be enrolled in Part A for subjects who discontinue the study due to treatment-related toxicity.

Cohort 1:

Part A

Eighteen to 24 subjects representing two age strata (at least 6 subjects must be 12 to < 15 years of age and at least 6 subjects must be 15 to < 18 years of age).

Part B

Twenty-six to 32 subjects between 12 to < 18 years of age (dependent upon enrollment in Part A).

Cohort 2:

Part A

Eighteen to 24 subjects 6 to < 12 years of age and weighing ≥ 25 kg.

Part B

Twenty-six to 32 subjects 6 to < 12 years of age and weighing ≥ 25 kg.

Cohort 3:

Approximately 25 subjects ≥ 2 years of age and weighing ≥ 14 to < 25 kg.

4.2. Inclusion Criteria

All Cohorts

Subjects must meet all of the following inclusion criteria, as well as the Cohort specific criteria listed below, to be eligible for participation in this study. Subjects with screening results that do not meet eligibility criteria will not be allowed to rescreen:

- CD4+ cell count ≥ 400 cells/μL and CD4+ percentage of 20%
- Adequate renal function: estimated glomerular filtration rate ≥ 90 mL/min/1.73 m^2
  - Estimated Glomerular Filtration Rate (eGFR) using Schwartz Formula (mL/min/1.73 m^2) = $k \times L/S_{cr}$ [(k is a proportionality constant, for females ≥ 2 years old is 0.55; and for males ≥ 12 years old is 0.70) and males and females 2 to ≤ 11 years old is 0.55; L is height in centimeters (cm); and S_{cr} is serum creatinine (mg/dL)]

- Clinically normal ECG (or if abnormal, determined by the investigator to be not clinically significant)
- Documented screening for active pulmonary tuberculosis per local standard of care within 6 months of a Screening visit.
- Hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin
- Adequate hematologic function:
  - Absolute neutrophil count ≥ 500/mm^3
  - Platelets ≥ 50,000/mm^3
  - Hemoglobin ≥ 8.5 g/dL
- Note that subjects with chronic neutropenia, defined as having an ANC of < 500/mm^3 documented at least twice within 6 months of screening, and in whom, according to the investigator, there is no evidence of active opportunistic or serious infection can enroll in the study contingent upon approval from the Gilead study Medical Monitor.
- Negative serum pregnancy test for all female subjects
- Females of childbearing potential (as defined in Appendix 5) must have a negative serum pregnancy test at screening and Baseline/Day 1
- Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5
- Subjects able to give written assent prior to any screening evaluations
- Parent or guardian able to give written informed consent prior to any screening evaluations and willing to comply with study requirements
- Able to swallow oral tablets
- Must be willing and able to comply with all study requirements
- Life expectancy > 1 year

Cohort 1

- 12 to < 18 years of age at Baseline
- Weight ≥ 35 kg (77 lbs) at Screening

- Plasma HIV-1 RNA levels of ≥ 1,000 copies/mL at Screening (Roche COBAS TaqMan v2.0)
- Screening genotype report shows sensitivity to EVG, FTC and TFV (Monogram Biosciences, Inc.)
  - Subjects with HIV subtype AE who meet all inclusion/exclusion criteria and who have a non-reportable integrase genotype result may proceed with study enrollment (Thailand only)
- No prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission)

Cohort 2

- 6 to < 12 years of age at Baseline
- Weight ≥ 25 kg (55 lbs) at Screening
- Plasma HIV-1 RNA: < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is > 50 copies/mL) for ≥ 180 consecutive days (6 months) prior to Screening on a stable antiretroviral regimen, without documented history of resistance to any component of E/C/F/TAF STR
  - Unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viremia, or "blip") prior to Screening is acceptable
  - Currently receiving an antiretroviral regimen that has been stable for at least 180 consecutive days (6 months) or has been newly initiated within 6 months for reasons other than virologic failure.

Cohort 3

- ≥ 2 years of age at Baseline
- Weight ≥ 14 to < 25 kg (≥ 31 to < 55 lbs) at Screening
- Plasma HIV-1 RNA: < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is > 50 copies/mL) for ≥ 180 consecutive days (6 months) prior to Screening on a stable antiretroviral regimen, without documented history of resistance to any component of E/C/F/TAF STR
  - Unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viremia, or "blip") prior to Screening is acceptable
  - Currently receiving an antiretroviral regimen that has been stable for at least 180 consecutive days (6 months) or has been newly initiated within 6 months for reasons other than virologic failure.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

- A new AIDS-defining condition diagnosed within the 30 days prior to Screening (Refer to Appendix 6).
- Positive Hepatitis C antibody. Note: Subjects with false positive hepatitis antibody confirmed by negative Hepatitis C PCR are permitted to enroll.
- Positive Hepatitis B surface antigen or other evidence of active HBV infection.
  Note: Subjects with positive HBV surface antibody and no evidence of active HBV infection are permitted to enroll.
- Prior treatment with any approved or investigational or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission) (Cohort 1 only)
- Evidence of active pulmonary or extra-pulmonary tuberculosis disease within 3 months of the Screening visit.
- Anticipated to require rifamycin treatment for mycobacterial infection while participating in the study. Note: prophylactic INH therapy for latent TB treatment is allowed.
- Subjects experiencing decompensated cirrhosis (e.g., ascites, encephalopathy, etc.)
- Pregnant or lactating subjects
- Have an implanted defibrillator or pacemaker
- Have any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include uncontrolled renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment within 30 days prior to the study dosing.
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance.
- Have history of significant drug sensitivity or drug allergy.
- Known hypersensitivity to the study drugs, the metabolites or formulation excipients (see Section 5.2)

- Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study Screening or expected to receive these agents during the study (e.g., immunoglobulins, and other immune- or cytokine-based therapies).
- A history of malignancy within the past 5 years (prior to Screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Baseline and must not be anticipated to require systemic therapy during the study.
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Baseline.
- Have previously participated in an investigational trial involving administration of any investigational agent within 30 days prior to the study dosing.
- Participation in any other clinical trial (including observational trials) without prior approval from sponsor is prohibited while participating in this trial.
- Subjects receiving ongoing therapy with any of the medications in the table below, including drugs not to be used with EVG, COBI, FTC, TDF and TAF (For EVG, COBI, and FTC refer to the individual agents Prescribing Information; for EVG, and TAF refer to the E/C/F/TAF STR Investigator's Brochure); or subjects with any known allergies to the excipients of E/C/F/TAF STR tablets.

Drug Class	**Agents Disallowed***
Alpha Adrenergic Receptor Antagonists	Alfuzosin
Antibacterials	Telithromycin
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
Antiplatelets	Clopidogrel
Endothelin Receptor Antagonists	Bosentan
Calcium Channel Blockers	Bepridil
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine
Direct Acting Anticoagulants	Apixaban, Rivaroxaban
GI Motility Agents	Cisapride
Herbal Supplements	St. John's Wort, Echinacea
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin
Neuroleptics	Pimozide
Sedatives/Hypnotics	Midazolam, Triazolam
Systemic** Corticosteroids with the exception of short-term (≤ 1 week) use of prednisone as a steroid burst	All agents, including dexamethasone

* Administration of any of the above medications must be discontinued at least 21 days prior to the Baseline/Day 1 visit and for the duration of the study.
** Systemic use defined as intravenously or orally administered corticosteroid.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

This is an open-label, non-blinded study. All eligible subjects will receive open-label E/C/F/TAF STR.

Once eligibility is confirmed, the Sponsor will assign a unique subject number for each eligible subject and provide the subject number information to the study site.

The subject number assignment may be performed up to 7 days prior to the in-clinic Baseline visit provided that all screening procedures have been completed and subject eligibility has been confirmed. Once a subject number has been assigned, it will not be reassigned to any other subject.

All Baseline tests and procedures must be completed and eligibility confirmed prior to the administration of the first dose of study drug.

It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment.

5.2. Description and Handling of E/C/F/TAF STR

5.2.1. Formulation

E/C/F/TAF 150/150/200/10 mg

E/C/F/TAF 150/150/200/10 mg STR tablets are capsule-shaped, film-coated green tablets and are debossed with "GSI" on one side of the tablet and "510" on the other side of the tablet. E/C/F/TAF STR tablets contain 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of TAF fumarate). The E/C/F/TAF 150/150/200/10 mg STR tablet cores contain silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate as inactive ingredients and are film-coated with indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

E/C/F/TAF 90/90/120/6 mg (Low Dose)

E/C/F/TAF LD STR tablets are capsule-shaped, film-coated green tablets and are debossed with "GSI" on one side of the tablet and "306" on the other side of the tablet. E/C/F/TAF LD STR tablets contain 90 mg of EVG, 90 mg of COBI, 120 mg of FTC, and 6 mg of TAF (as 6.7 mg of TAF fumarate). The E/C/F/TAF LD STR tablet cores contain silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate as inactive ingredients and are film-coated with polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, black iron oxide, and yellow iron oxide.

If clinical supply is discontinued, sites will be able to use both clinical and commercial supplies of E/C/F/TAF STR. Low dose tablets intended for commercial use are similar in appearance and the same in composition as tablets provided via the clinical supply chain. Clinical and commercial E/C/F/TAF LD tablets are debossed with "GSI" on one side of the tablet; the other side of the tablet is debossed with "306" for clinical E/C/F/TAF LD tablets while the commercial E/C/F/TAF LD tablets are scored.

5.2.2. Packaging and Labeling

E/C/F/TAF 150/150/200/10 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant canister and polyester coil fiber. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

E/C/F/TAF 90/90/120/6 mg LD tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, a silica gel desiccant canister and polyester coil fiber. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

All labels for study drug bottles to be distributed to centers in all countries will meet all applicable requirements of the FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

5.2.3. Storage and Handling

The E/C/F/TAF STR tablets should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). To ensure the stability of the tablets, the drug product should not be dispensed into a container other than the container in which it is supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

All study medications should not be stored in any containers other than the container in which it is supplied.

5.3. Dosage and Administration of E/C/F/TAF STR

The E/C/F/TAF STR tablets will be provided by Gilead Sciences and will be administered orally, once daily with food at approximately the same time each day.

In-clinic dosing will be performed at Baseline/Day 1 and Weeks 1, 2, 4, 12, 24, and 48. For those subjects that take their medication in the evening, the in-clinic dosing will not be performed.

Subjects in Part A (inclusive of Cohort 3) will be administered their dose of study medication in the clinic with food during the Intensive PK visit, at Week 4 (Cohorts 1 and 2) or Week 2 (Cohort 3). In order to allow for ease of PK sampling over a 24-hour period, subjects should be instructed to take their dose of E/C/F/TAF STR together with food at the same time every day **in the morning (breakfast)**, during the days leading up to Intensive PK assessments.

Prior to the scheduled trough and Intensive PK visits, subjects should fast overnight (a minimum of 8 hours).

After Week 48, all subjects receiving E/C/F/TAF STR who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study. Subjects will return 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, subjects will return for study visits every 24 weeks for the duration of the extension phase.

Subjects will be instructed to bring all study medication in the original container at each study visit for drug accountability (unless otherwise specified in Section 6). The investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. The inventory and dispensing logs must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return. Remote drug accountability will be permitted in instances where on-site drug accountability is not possible and will require prior Gilead approval.

After collection of intensive PK samples at Week 2, dose adjustments are permitted for subjects in Cohort 3 due to weight changes, including during the extension phase. A subject whose weight has increased to ≥ 25 kg when measured at a study visit may have their dose increased to E/C/F/TAF 150/150/200/10 mg at that visit. If the subject's weight is < 25 kg at a subsequent visit, dose reduction back to E/C/F/TAF 90/90/120/6 mg may be implemented at the investigator's discretion.

For subjects in Cohort 3 unable to swallow the tablet whole, it is acceptable to split the tablet in two and administer both parts sequentially.

5.4. Prior and Concomitant Medications

- Concentrations of ethinyl estradiol may decrease and progestin level may increase on coadministration of hormonal contraceptives with study drug. Please see the table below and refer to Appendix 5 for guidance on the use of contraception methods.
- Coadministration of Genvoya with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of the active metabolite(s).
- Drugs that induce CYP3A activity are expected to increase the clearance of EVG and COBI, resulting in decreased plasma concentration of COBI, and thus that of EVG, which may lead to loss of therapeutic effect of Genvoya, and development of resistance.
- Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study due to potential drug-drug interactions with the study drug. Inclusion of medications in this list does not imply approval for use in pediatric populations.
- The list below should be utilized in jurisdictions in which E/C/F/TAF has NOT been approved.

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Acid Reducing Agents Antacids		Elvitegravir plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate E/C/F/TAF STR and antacid administration by at least 2 hours.
Alpha-1 Adrenoreceptor Antagonist	Alfuzosin	
Antiarrhythmics		Amiodarone, Bepridil, Digoxin, Disopyramide, Flecainide, systemic Lidocaine, Mexiletine, Propafenone, Quinidine: Concentrations of these antiarrhythmics may increase when coadministered with Cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with E/C/F/TAF STR.
Antibacterials	Telithromycin	Clarithromycin and Telithromycin: Concentrations of Clarithromycin and/or Cobicistat may be altered when Clarithromycin is coadministered with E/C/F/TAF STR. Patients with CL_{cr} greater than or equal to 60 mL/min: No dose adjustment of Clarithromycin is required. Patients with CL_{cr} between 30 mL/min and 60 mL/min: The dose of Clarithromycin should be reduced by 50%. Concentrations of Telithromycin and/or Cobicistat may be increased when Telithromycin is coadministered with E/C/F/TAF STR. Clinical monitoring is recommended upon coadministration with E/C/F/TAF STR.
Anticoagulants		Concentrations of Warfarin may be affected upon coadministration with E/C/F/TAF STR. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with E/C/F/TAF STR.
Direct Oral Anticoagulants (DOACs)	Apixaban, Rivaroxaban	Dabigatran, Edoxaban: Concentrations may increase with study drug(s). Clinical monitoring and/or dose adjustment is recommended
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoin,	Ethosuximide, Oxcarbazepine, Coadministration of Oxcarbazepine, a CYP3A inducer, may decrease Cobicistat and Elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. Concentrations of Ethosuximide may be increased when coadministered with Cobicistat. Clinical monitoring is recommended upon coadministration with E/C/F/TAF STR.
Antidepressants		Bupropion: Concentrations may increase or decrease with study drug. Subjects receiving bupropion should be monitored for adequate clinical response. SSRI dosing should be titrated in conjunction with clinical monitoring. SSRIs except Sertraline, and Trazodone, tricyclic antidepressants (TCAs): Concentrations may increase when coadministered with Cobicistat. Concentrations of Sertraline are not affected upon coadministration with study drug. No dose adjustment is required upon coadministration. Concentrations of other antidepressant agents may be increased when coadministered with Cobicistat. Dose titration may be required for most drugs of the SSRI class. Concentrations of Trazodone may increase upon coadministration with Cobicistat. Dose reduction should be considered when Trazodone is coadministered with E/C/F/TAF STR.

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Antifungals		Concentrations of ketoconazole, itraconazole and/or cobicistat may increase with coadministration of E/C/F/TAF STR. When administering with E/C/F/TAF STR, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day. Concentrations of voriconazole may be increased when coadministered with cobicistat. Clinical monitoring may be needed upon coadministration with E/C/F/TAF STR.
Antigout		Colchicine: Concentrations may increase with study drug(s). Dose reductions of colchicine may be required. Should not be coadministered in patients with renal or hepatic impairment. Dose reductions of colchicine may be required. E/C/F/TAF STR should not be coadministered with colchicine in patients with renal or hepatic impairment. Treatment of familial Mediterranean fever: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
Antihistamines		Astemizole, Terfenadine: Concentrations of Astemizole and Terfenadine may be increased when coadministered with Cobicistat. Clinical monitoring is recommended when these agents are coadministered with E/C/F/TAF STR.
Antimycobacterials	Coadministration of rifampin, rifabutin, and rifapentine, potent CYP3A inducers, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of E/C/F/TAF STR with rifampin is contraindicated. Coadministration of E/C/F/TAF STR with rifabutin or rifapentine is not recommended.	
Antiplatelets	Coadministration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel. Coadministration of clopidogrel with Genvoya is not recommended. Genvoya is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.	
Benzodiazepines	Orally administered Midazolam and Triazolam	Diazepam: Concentrations of other benzodiazepines, including Diazepam and parenterally administered Midazolam, may be increased when administered with E/C/F/TAF STR. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction may be necessary. Based on non-CYP-mediated elimination pathways for Lorazepam, no effect on plasma concentrations is expected upon coadministration with E/C/F/TAF STR.
β-Blockers		Concentrations of beta-blockers may be increased when coadministered with Cobicistat. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with E/C/F/TAF STR.

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Calcium Channel Blockers		Amlodipine, Diltiazem, Felodipine, Nicardipine, Nifedipine, Verapamil: Concentrations of calcium channel blockers may be increased when coadministered with Cobicistat. Caution is warranted and clinical monitoring is recommended upon coadministration with E/C/F/TAF STR.
Corticosteroids		Betamethasone, Budesonide, Dexamethasone (oral), Fluticasone, Mometasone, Triamcinolone: Coadministration of dexamethasone, a CYP3A inducer, may decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered. Coadministration with corticosteroids that are sensitive to CYP3A inhibition can increase the risk for Cushing's syndrome and adrenal suppression, which have been reported during postmarketing use of cobicistat-containing products. Consider the risk of systemic corticosteroid effects if E/C/F/TAF STR is coadministered with corticosteroids that are sensitive to CYP3A inhibition. Alternative corticosteroids should be considered, particularly for long-term use. For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.
Endothelin Receptor Antagonists		Coadministration of Bosentan with study drug may lead to decreased Elvitegravir and/or Cobicistat exposures and loss of therapeutic effect and development of resistance. Alternative endothelin receptor antagonists may be considered.
Ergot Derivatives	Ergotamine, Ergonovine (known as ergometrine in some regions), Dihydroergotamine Methylergonovine	
GI Motility Agents	Cisapride	
Hepatitis C Virus Antiviral Agents		Concentrations of Cobicistat, Ledipasvir, Sofosbuvir, and GS-331007 (the predominant circulating metabolite of sofosbuvir) are increased when ledipasvir/sofosbuvir is coadministered with Elvitegravir and Cobicistat. The effect of coadministration of ledipasvir/sofosbuvir and E/C/F/TAF STR on concentrations of all components of these fixed-dose combinations is unknown. There are insufficient data to make a dosing recommendation for coadministration of E/C/F/TAF STR with ledipasvir/sofosbuvir.
Herbal/Natural Supplements	St. John's Wort	
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin	Concentrations of Atorvastatin may be increased when coadministered with Elvitegravir and Cobicistat. Start with the lowest possible dose of Atorvastatin with careful monitoring upon coadministration with E/C/F/TAF STR. Concentrations of Rosuvastatin are transiently increased when coadministered with Elvitegravir and Cobicistat. Dose modifications are not necessary when Rosuvastatin is administered in combination with E/C/F/TAF STR.
Hormonal Contraceptives		Drospirenone: Plasma concentrations may be increased when administered with E/C/F/TAF STR. Clinical monitoring is recommended due to the potential for hyperkalemia. Coadministration of study drug and a norgestimate/ethinyl estradiol-containing hormonal oral contraceptive is expected to decrease plasma concentrations of ethinyl estradiol and increase norgestimate. Use caution when coadministering study drug and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol..

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
		The long-term effects of substantial increases in progesterone exposure are unknown. The effect of coadministration of E/C/F/TAF STR with oral contraceptives or hormonal contraceptives containing progestogens other than drospirenone, norgestimate, or less than 25 mcg of ethinyl estradiol, is not known
Immunosuppressants		Cyclosporine, Rapamycin, Sirolimus, Tacrolimus: Concentrations may increase when coadministered with Cobicistat. Therapeutic monitoring is recommended upon coadministration with E/C/F/TAF STR.
Inhaled Beta Agonist		Salmeterol: Coadministration with study drug may result in increased plasma concentrations of Salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of Salmeterol and E/C/F/TAF STR is not recommended.
Neuroleptics	Pimozide	Perphenazine, Risperidone, Thioridazine, Quetiapine: Consider reducing the dose of the neuroleptic upon coadministration with E/C/F/TAF STR.
Phosphodiesterase-5 Inhibitors	Coadministration of E/C/F/TAF STR with Sildenafil for the treatment of pulmonary arterial hypertension (PAH) is contraindicated.	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with E/C/F/TAF STR may result in increased plasma concentrations of Sildenafil and Tadalafil, which may result in PDE5 inhibitor-associated adverse reactions. Caution should be exercised, including consideration of dose reduction, when coadministering E/C/F/TAF STR with Tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered with E/C/F/TAF STR.
Sedatives/Hypnotics	Midazolam, Triazolam	Buspirone, orally administered Zolpidem: With sedative/hypnotics, dose reduction may be necessary upon coadministration with E/C/F/TAF STR and clinical monitoring is recommended.

In jurisdictions in which E/C/F/TAF has been approved, consult the local prescribing information for E/C/F/TAF dose recommendations with concomitant medications.

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead Science Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication.

5.5. Study Drug Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of

the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during a monitoring visit prior to disposal or return of study drug. Performing drug accountability at an on-site monitoring visit is preferred; however, if necessary, remote drug accountability can be performed with prior approval from Gilead.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2, and also described in the text that follows.

All subjects will participate in all study visits and assessments. Additionally, subjects in Part A (inclusive of Cohort 3) will complete the Intensive PK visit at Week 4 (Cohorts 1 and 2) or Week 2 (Cohort 3).

Any deviation from protocol procedures should be noted and the Sponsor or Contract Research Organization (CRO) should be notified.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment.

Please refer to Section 5.1 for details about subject number assignment.

6.2. Screening Visit

Each subject must sign an assent (and parent or legal guardian sign an informed consent form) prior to the conduct of any screening procedures. Subjects will be assigned a screening number at the time of assent/consent. Screening evaluations are used to determine the eligibility of each candidate for study enrollment.

The following evaluations are to be completed at the Screening visit:

- Obtain medical and medication history, including history of HIV-1 disease-related events, and any other ongoing medications within 30 days of the Screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- 12-lead ECG performed supine
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - For Cohort 3, urine renal safety including: urine chemistry, retinol binding protein and beta-2-microglobulin.

- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled.
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, CPK, and uric acid
  - For Cohort 3, metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, high-density lipoprotein [HDL], direct low-density lipoprotein [LDL], and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Estimated Glomerular Filtration Rate (GFR) using Schwartz Formula (mL/min/1.73 m^2) = $k \times L/S_{cr}$
  - Plasma HIV-1 RNA (Roche COBAS TaqMan® v2.0)
  - Whole blood sample (Cohort 3 only)
  - Full flow cytometry panel testing
  - HIV-1 genotype (protease, reverse transcriptase and integrase) testing (Cohort 1 only). The HIV-1 genotype may not be performed for subjects that fail to meet other screening laboratory criteria.
  - Hepatitis B virus (HBV) surface antigen serology (HBsAg)
  - Hepatitis C virus (HCV) serology (HCVAb)
  - For Cohort 3, serum bone safety including: Bone specific alkaline phosphatase, parathyroid hormone (PTH), 25OH Vitamin D, and 1,25OH Vitamin D
- Review of Adverse Events (AEs) and Concomitant Medications
- Historical genotype report(s) should be collected, if available (Cohorts 2 and 3 only)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days after the Screening visit for the Baseline/Day 1 assessments. For Cohort 1, the Screening window may be extended to 42 days for subjects who require repeat testing of the HIV-1 genotype.

Subjects with exclusionary screening laboratory results due to an acute clinical condition which resolves can be re-screened within 3 months of initial Screening. The decision to re-screen the subject will be made in consultation with the Medical Monitor, and written notice of eligibility from the Sponsor is required before a re-screened subject can be enrolled.

For each screened subject, complete an eligibility worksheet and submit to Sponsor for review prior to assignment of subject number. The subject number assignment may be performed up to 7 days prior to the in-clinic Baseline visit provided that all other Screening procedures have been completed and subject eligibility has been confirmed.

6.3. Treatment Assessments

6.3.1. Baseline/Day 1 Assessments

The following evaluations are to be completed at the Baseline/Day 1 visit. The subject must complete all Baseline procedures before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Baseline visit. For Cohort 1, the investigator must have received the results from the screening genotype report before proceeding with the Baseline/Day 1 visit.

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- Tanner Stage assessments (≥ 6 years of age)
- DXA Scan (lumbar spine and total body)
    - The DXA scan will be performed on subjects once eligibility is confirmed and prior to study drug administration at the Baseline/Day 1 visit. The scan may be performed on the morning of the Baseline/Day 1 visit as long as it occurs before dosing.
- Urine collection for the following laboratory procedures:
    - Urinalysis
    - For Cohorts 1 and 2, urine renal safety including: urine chemistry, retinol binding protein and beta-2-microglobulin.
    - For Cohorts 1 and 2, urine bone safety including: bicarbonate, N-telopeptide

- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at Baseline, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will not be able to participate.

- Urine sample storage for possible additional testing (Urine chemistry including urine phosphorus and urine creatinine)

- Blood sample collection for the following laboratory analyses:

  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, cystatin C for Cohorts 1 and 2, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, phosphorus, magnesium, potassium, sodium, CPK, and uric acid

  - For Cohorts 1 and 2, metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

  - Hematology profile: CBC with differential and platelet count

  - Plasma HIV-1 RNA (Roche COBAS TaqMan® v2.0)

  - Full flow cytometry panel testing

  - Plasma storage sample for possible additional testing (virology analysis, safety, pharmacokinetic analysis) (Cohorts 1 and 2)

  - For Cohorts 1 and 2, serum bone safety including: Bicarbonate, N-telopeptide, C-telopeptide (CTX), osteocalcin, procollagen type 1 N-terminal propeptide (P1NP), bone specific alkaline phosphatase, parathyroid hormone (PTH), 25OH Vitamin D, and 1,25OH Vitamin D

  - Estimated glomerular filtration rate according to Schwartz formula

- Study drug dispensation. Subjects should initiate dosing of study drug along with food in-clinic the day of the Baseline visit.

- Subjects should be instructed to take study drugs with food. The subject should be counseled regarding the importance of adherence and taking their study medication at approximately the same time each day as directed by the investigator. Sites should consider individual subject study drug dosing schedule while scheduling study visits requiring collection of trough PK samples.

- The PK study of Part A (inclusive of Cohort 3) is designed to assess the PK of and confirm the doses of E/C/F/TAF STR. Therefore, all subjects must take their dose of study medication with food at approximately the same time every morning at all visits prior to the Intensive PK visit.

- Palatability and Acceptability assessment (Cohorts 2 and 3)
  - The investigator will ask if the study drug was palatable and if the subject was able to take the dosage form.

- Subjects should be reminded to bring the required drug bottles of the E/C/F/TAF STR with them for in-clinic dosing and drug accountability at the Week 1/(Day 7) visit.

6.3.2. Treatment Assessments through 48 Weeks (Weeks 1 (Day 7) – 48)

The following evaluations are to be completed at the end of Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40 and 48 unless otherwise specified.

All study visits are to be scheduled relative to the Baseline/Day 1 visit date. The Week 1 (Day 7) visit should occur on the protocol-specified visit date based on the Baseline/Day 1 visit. Study visits at Weeks 2 through 8 are to be completed within ± 2 days of the protocol-specified visit date based on the Baseline/Day 1 visit and completed within ± 4 days of the protocol-specified visit date at Weeks 12 through Week 48, unless otherwise specified.

Regularly scheduled evaluations will be made on all subjects whether or not they continue to receive study drug.

- Review of AEs and changes in concomitant medications

- Complete physical examination (**Weeks 24 and 48**) (urogenital/anorectal exams will be performed at the discretion of the investigator) or symptom-directed physical examination as needed (**all other visits**)

- Vital signs (blood pressure, pulse, respiration rate, and temperature)

- Height and weight

- Tanner Stage assessments for ≥ 6 years of age (**Weeks 24 and 48 −** except for subjects documented to have achieved Tanner Stage 5)

- DXA scan (lumbar spine and total body) (**Weeks 24 and 48 ± 10 days**)

- Urine collection for the following laboratory procedures:
  - Urinalysis and urine chemistry
  - Urine renal safety including: urine chemistry, retinol binding protein and beta-2-microglobulin (**Weeks 8, 12, 24, and 48**)

- For Cohorts 1 and 2, urine bone safety including: bicarbonate, N-telopeptide (**Weeks 8, 12, 24, and 48**)
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued
- Urine sample storage for possible additional testing (Urine chemistry including urine phosphorus and urine creatinine)

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, cystatin C (**Weeks 2 [Cohort 1 only], 4, 24, and 48 [Cohorts 1 and 2 only]. Cystatin C will not be done for Cohort 3 to reduce blood draw volumes**), total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid. At Weeks 24 and 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
  - Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments (**Weeks 24 and 48 only**).
  - Hematology profile: CBC with differential and platelet count
  - Plasma HIV-1 RNA (Roche COBAS TaqMan v2.0)
  - Full flow cytometry panel testing (Weeks 2 – 48)
  - Plasma storage sample for possible additional testing (virology analysis, safety, pharmacokinetic analysis) (**Week 4 [Cohort 1 Part B subjects only], Weeks 8-48 [all cohorts], and Week 32 [Cohorts 1 and 2 only]**)
  - Serum bone safety including:

    Cohorts 1 and 2: bicarbonate, N-telopeptide, CTX, osteocalcin, P1NP

    For all cohorts: bone specific alkaline phosphatase, PTH, 25OH Vitamin D, and 1,25OH Vitamin D (Weeks 8 [Cohort 1 only], 12, 24 and 48)
  - Estimated glomerular filtration rate according to Schwartz formula
  - HIV-1 genotype/phenotype testing for subjects with suboptimal virologic response or virologic rebound (as needed)

- Pharmacokinetic (PK) blood collection:

  Cohort 1

  — Trough PK sample (20 to 24 hours post-dose) (**Weeks 1 (Day 7), 2, 24, and 48**)*

  — Timed Single PK sample collected between 0.25 to 4 hours post-dose (**Week 4 [Part B subjects only] and at Week 12 only**)*

  — Random Single PK sample taken anytime in relationship to last dose of study drug (**all other visits**)*

  Cohort 2

  — Trough PK sample (20 to 24 hours post-dose) (**Weeks 1, 2, and 24**)

  — Timed Single PK sample collected between 0.25 to 4 hours post-dose (**Week 12 only**)*

  — Random Single PK sample taken anytime in relationship to last dose of study drug (**Weeks 8 and 16**)

  Cohort 3

  — Timed Single PK sample collected between 0.25 to 4 hours post-dose (**Weeks 8, 12, and 16**)*

  — Trough PK sample (20 to 24 hours post-dose). Subjects should be reminded not to take their study medication on the morning of these visits. The time of last dose prior to the PK draw should be documented. (**Weeks 4 and 24**)

  * For subjects who take their medication in the evening, a Random Single PK sample taken at any time in relationship to last dose of study drug will be collected in lieu of the Trough or Timed Single PK collected between 0.25 to 4 hours post-dose. The time of last dose prior to the PK draw should be documented. (**For Uganda only**)

- Subjects who meet the criteria for suboptimal virologic response or rebound should be managed according to Management Virologic Failure Section 6.8.1.

- Subjects should be reminded not to take their study medication on the morning of their Week 1 (Day 7), 2, 4, 12, 24, and 48 clinic visits and the visits during which PK trough or intensive samples will be collected.

- Document study drug dispensation and accountability for all study drugs dispensed. No study drug will be dispensed at the Week 2 visit.

- Subject dosing diaries should be dispensed at the Week 1 (Cohort 3) or Week 2 (Cohorts 1 and 2) visit (depending upon the timing of the intensive PK visit) to subjects in Part A (inclusive of Cohort 3) to capture study drug information prior to the Intensive PK study visit.

- Palatability and Acceptability Assessment

  — For Cohort 1, at the next scheduled visit, the investigator will ask if the study drug was palatable and if the subject was able to take the dosage form. If the subject has passed the Week 48 visit, the assessment will be performed during the next scheduled post Week 48 visit. If the subject discontinues prior to the Week 48 visit, this assessment will be captured at the ESDD visit.

  — For Cohort 2, the same questions asked at Baseline will be asked at Week 4 or if the subject discontinues prior to the Week 4 visit, this assessment will be captured at the ESDD visit.

  — For Cohort 3, the same questions asked at Baseline will be asked at Week 4, Week 24, and Week 48. If the subject discontinues prior to the Week 4 visit, this assessment will be captured at the ESDD visit.

6.3.3. Intensive PK Evaluation (Part A subjects 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.

Subjects should come in a fasted state (i.e. no food or drink except water at least 8 hours prior). Subjects should be instructed that on the day of the Intensive PK evaluation the dose of E/C/F/TAF STR must not be taken prior to the visit.

If the subject 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 subject 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 assessments.

If dosing non-compliance not related to AEs is identified on or prior to the Intensive PK evaluation visit, the Intensive PK assessments must not be completed. The subject should be counseled regarding proper dosing and be scheduled to return for the Intensive PK evaluation visit no sooner than three days following compliant dosing and no later than Week 4 (Cohorts 1 and 2) + 7 days or Week 2 (Cohort 3) + 7 days.

In both scenarios described above, the subject should be reminded to not take the E/C/F/TAF STR prior to arriving at the clinic on the day of the re-scheduled Intensive PK visit. All Intensive PK assessments listed below should be completed when the subject returns:

- Subject dosing diaries will be collected and reviewed.

- For Cohort 1 subjects, blood samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing). After collection of the pre-dose sample, subjects will be provided a standardized meal. **Within five minutes after consuming the standardized meal**, subjects will be dosed with the E/C/F/TAF STR. Intensive PK sampling at the following time-points will occur: 5 minutes, 0.25, 0.5, 1, 1.5, 2, 4, 5, 8 and 24 hours post-dose.

- For Cohort 2 subjects, blood samples will be collected ≤ 30 minutes prior to dosing. After collection of the pre-dose sample, subjects will be provided a meal. **Within five minutes after consuming the meal**, subjects will be dosed with the E/C/F/TAF STR. Intensive PK sampling at the following time-points will occur: 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours post-dose. Subjects will be restricted from further food intake until after the 4-hour PK blood draw.

- For Cohort 3 subjects, blood samples will be collected ≤ 30 minutes prior to dosing. After collection of the pre-dose sample, subjects will be provided a meal. **Within five minutes after consuming the meal**, subjects will be dosed with the E/C/F/TAF STR. Intensive PK sampling at the following time-points will occur: 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 8 hours post-dose. Subjects will be restricted from further food intake until after the 4-hour PK blood draw.

CCI [redacted]

[redacted]

6.3.5. Post-Week 48 Assessments

Study subjects receiving E/C/F/TAF STR who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study where Gilead will provide E/C/F/TAF STR until: a) the relevant E/C/F/TAF STR formulation is available for use, other than through the study, in the country in which the subject is enrolled, or b) Gilead Sciences elects to terminate development of E/C/F/TAF STR in the applicable country. Subjects who are no longer taking study drug at Week 48 are not eligible to participate in the study extension.

6.3.5.1. Post-Week 48 through Week 240 for Cohorts 1 and 2 and Post-Week 48 through Week 96 for Cohort 3

Subjects who choose to receive the E/C/F/TAF STR or E/C/F/TAF LD STR in the extension phase will return for study visits every 12 weeks through Week 240 for Cohorts 1 and 2 and through Week 96 for Cohort 3. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.

The following evaluations are to be completed at visits every 12 weeks unless otherwise specified:

- Review of AEs and concomitant medications
- Tanner Stage assessments (subjects ≥ 6 years of age) (every 48 weeks - except for subjects documented to have achieved Tanner Stage 5)
- Symptom-directed physical examination as needed

- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- Urine collection for the following procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued.
  - Urine sample storage for possible additional testing
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid
  - Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. **(every 48 weeks)**
  - Estimated glomerular filtration rate according to Schwartz formula
  - Hematology profile: CBC with differential and platelet count
  - Full flow cytometry panel testing
  - Plasma HIV-1 RNA (Roche COBAS TaqMan v2.0)
  - Plasma storage sample for possible additional testing (virology analysis, safety, pharmacokinetic analysis)
  - Serum bone safety **(every 24 weeks)** including:

    Cohorts 1 and 2: bicarbonate, N-telopeptide, CTX, osteocalcin, P1NP

    For all cohorts: bone specific alkaline phosphatase, PTH, 25OH Vitamin D, and 1,25OH Vitamin D
- DXA scan (lumbar spine and total body) (**every 48 weeks ± 10 days**)
- Study drug dispensation

- Study drug accountability
- Palatability and Acceptability assessment **(Cohort 1 only)**
  - At the next scheduled visit, the investigator will ask if the study drug was palatable and if the subject was able to take the dosage form.

6.3.5.2. Post-Week 240 for Cohorts 1 and 2 and Post-Week 96 for Cohort 3

Subjects who choose to receive the E/C/F/TAF STR or E/C/F/TAF LD STR in the extension phase after Week 240 in Cohorts 1 and 2 and after Week 96 in Cohort 3 will return for study visits every 24 weeks for the duration of the extension phase. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified. Subjects should be fasting (no food or drinks, except water, at least 8 hours prior to blood collection).

The following evaluations are to be completed at visits every 24 weeks unless otherwise specified:

- Review of AEs and concomitant medications
- Tanner Stage assessments (subjects ≥ 6 years of age) (every 48 weeks - except for subjects documented to have achieved Tanner Stage 5)
- Symptom-directed physical examination as needed
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- Urine collection for the following procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued.
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, fasting glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid
  - Estimated glomerular filtration rate according to Schwartz formula
  - Hematology profile: CBC with differential and platelet count
  - CD4 cell count and percentage

- Plasma HIV-1 RNA (Roche COBAS TaqMan v2.0)
- Plasma storage sample for possible additional testing (virology analysis, safety, pharmacokinetic analysis)
- Serum bone safety including **(Cohort 3)**:
  - Bone specific alkaline phosphatase, PTH, 25OH Vitamin D, and 1,25OH Vitamin D. (**every 48 weeks from Week 96 up to and including Week 240**)

- DXA scan (lumbar spine and total body) (**Cohort 3 only**) (**every 48 weeks ± 10 days up to and including Week 240**)
- Study drug dispensation
- Study drug accountability

6.3.6. Early Study Drug Discontinuation (ESDD)

If a subject in the treatment phase of the study discontinues study drug prior to Week 48, the subject will be asked to return to the clinic within 72 hours of stopping study drugs for an ESDD Visit. Subjects will then be asked to continue attending all scheduled study visits. Subjects who are no longer taking study drug at Week 48 are not eligible to participate in the study extension.

At the ESDD Visit, any evaluations showing abnormal results for which there is a possible or probable causal relationship with the study drug, should be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The following evaluations are to be completed at the ESDD visit:

- Review of AEs and concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator)
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- Urine collection for the following procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). The positive result will be confirmed with a serum pregnancy test.
  - Urine sample storage for possible additional testing (Urine chemistry including urine phosphorus and urine creatinine)

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid
  - Estimated glomerular filtration rate according to Schwartz formula
  - Hematology profile: CBC with differential and platelet count
  - Full flow cytometry panel testing
  - Plasma HIV-1 RNA (Roche COBAS TaqMan v2.0)
  - Plasma storage samples for virology testing, safety or pharmacokinetic testing
  - Serum storage sample for possible additional testing
  - HIV-1 genotype/phenotype testing for subjects with suboptimal virologic response or virologic rebound
  - Single plasma PK sample taken anytime in relationship to last dose of study drug
- Study drug accountability
- Palatability and Acceptability assessment (if applicable)

6.3.7. 30-Day Follow-Up Visit

Subjects who discontinue study drug prior to Week 48 will be required to return to the clinic 30 days after completion of an Early Study Drug Discontinuation Visit for a 30-Day Follow-Up Visit. Those subjects who permanently discontinue study drug and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30-Day Follow-Up Visit.

Subjects who complete 48 weeks on study drug will be required to return to the clinic 30 days after completion of the Week 48 visit for a 30-Day Follow-Up Visit only if they do not wish to enroll in the extension phase of the study.

Subjects who complete 48 weeks and continue in the extension phase will be required to return to the clinic 30 days after discontinuation of study drug for a 30-Day Follow-Up Visit.

For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. The following evaluations are to be completed at the 30-Day Follow-Up Visit:

- Review of AEs and concomitant medications
- Symptom-directed physical examination, if indicated

- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Height and weight
- Urine collection for the following procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). A positive result will be confirmed with a serum pregnancy test.
  - Urine sample storage for possible additional testing (Urine chemistry including urine phosphorus and urine creatinine)
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid
  - Estimated glomerular filtration rate according to Schwartz formula
  - Hematology profile: CBC with differential and platelet count
  - Full flow cytometry panel testing
  - Plasma HIV-1 RNA (Roche COBAS TaqMan v2.0)
  - Serum storage sample for possible additional testing
- Palatability and Acceptability assessment (if applicable)

At the 30-Day Follow-Up Visit, any evaluations showing abnormal results for which there is a possible or probable causal relationship with the study drug, should be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

6.4. Bone Evaluations

Dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body will be performed prior to study drug administration at the Baseline/Day 1, and Weeks 24, 48 and applicable post-Week 48 visits (±10 days). Scans will measure changes in lumbar spine bone mineral density (BMD) and total BMD. DXA scan results will be provided to study sites.

A complete description of the procedures performed for the DXA scans will be provided in a DXA manual.

6.5. Bone and Renal Safety

The following serum bone safety parameters will be collected at Screening (Cohort 3) or Baseline (Cohorts 1 and 2) and Weeks 8 (Cohort 1 only), 12, 24, and 48 and applicable post-Week 48 visits (±6 days): Serum: For Cohorts 1 and 2 only: bicarbonate, N-telopeptide, C-telopeptide (CTX), osteocalcin, and procollagen type 1 N-terminal propeptide (P1NP). For all cohorts: bone specific alkaline phosphatase, PTH, 25OH Vitamin D, and 1,25OH Vitamin D.

For Cohorts 1 and 2, the following urine bone safety parameters will be collected at Baseline, Weeks 8, 12, 24, 48: Urine: bicarbonate, N-telopeptide.

For all subjects, urine will also be collected for selected renal safety, including urine chemistry, retinol binding protein, and beta-2-microglobulin at the Screening (Cohort 3) or Baseline (Cohorts 1 and 2) visit, and Weeks 8, 12, 24, 48.

6.6. Plasma and Urine Storage

A portion of the blood and urine samples drawn at specific visits will be frozen and stored, as noted in Appendix 2, Study Procedures Table. These stored blood and urine samples may be used by the Sponsor or its research partners for HIV-1 genotyping/phenotyping assays or their development, for retesting the amount of HIV-1 in the blood, for measurement of antiviral drug levels in the blood, CCI [redacted] or clinical laboratory testing to provide additional safety data. CCI [redacted]

6.7. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Lack of efficacy (virologic failure)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/independent ethics committee (IEC)

6.8. Virologic Failure

Subjects in Cohort 1 who experience suboptimal virologic response (SVR) or subjects in Cohorts 1, 2, or 3 who experience virologic rebound (VR), as defined below, will be considered to have virologic failure.

Upon confirmation of virologic failure, potential causes should be documented. Assessments should include:

- Adherence
- Concomitant medication
- Comorbidities (eg active substance abuse, depression, other intercurrent illnesses)

If virologic failure is confirmed and the HIV-1 RNA value is ≥ 400 copies/mL, the blood samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing.

Genotype/phenotype resistance testing will be performed using the RT/PR PhenoSense GT assay, the IN GeneSeq assay, and the IN PhenoSense assay (Monogram Biosciences, Inc.) in subjects who experience suboptimal virologic response or virologic rebound, if HIV-1 RNA is ≥ 400 copies/mL.

If genotype/phenotype resistance to study drug is documented, study drugs should be discontinued.

If no resistance is detected from genotype/phenotype testing, the subject may remain on study drug and an HIV-1 RNA test should be repeated (3-6 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Medical Monitor prior to study drug discontinuation.

6.8.1. Management of Suboptimal Virologic Response (Cohort 1 only)

Subjects who meet the criteria listed below will be considered to have suboptimal virologic response:

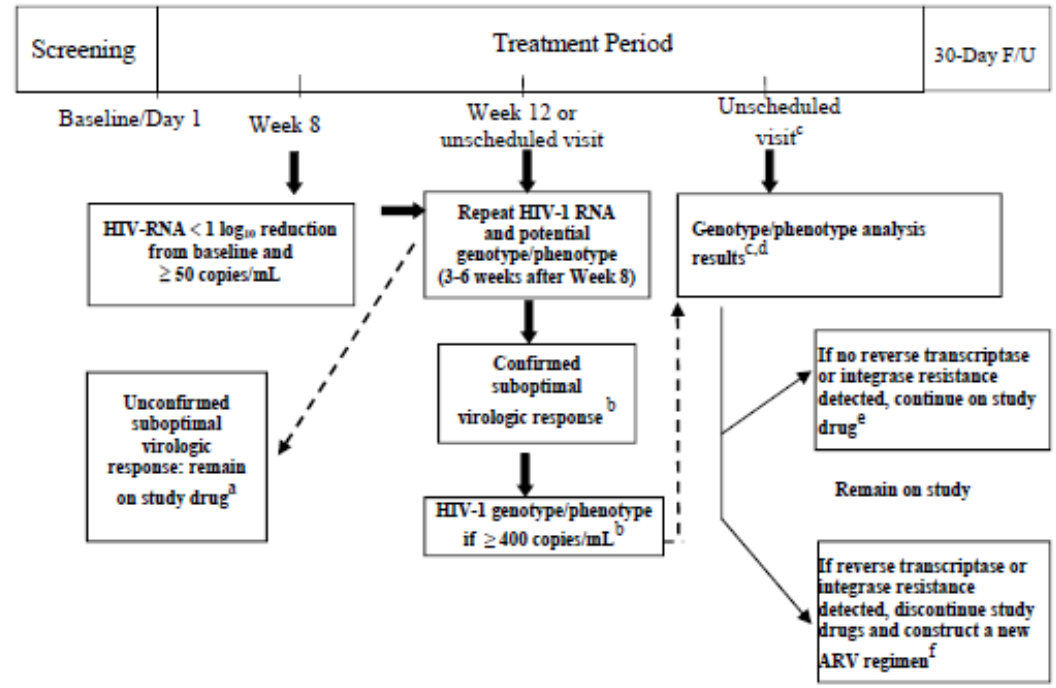
- HIV-1 RNA is < 1 $\log_{10}$ reduction from Baseline **and** ≥ 50 copies/mL at the Week 8 visit, confirmed at Week 12 or Unscheduled visit following Week 8.

Following the unconfirmed suboptimal virologic response at Week 8, HIV-1 RNA should be repeated at a scheduled or Unscheduled visit (3-6 weeks after the date of the original test with HIV-1 RNA to ≥ 50 copies/mL). If suboptimal virologic response is confirmed, the samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing if HIV-1 RNA is ≥ 400 copies/mL.

Please refer to Figure 6-1 for the management of subjects who meet the criteria for suboptimal virologic response.

Figure 6-1. Suboptimal Virologic Response Schema (Cohort 1 only)

Figure 6-1. Suboptimal Virologic Response Schema (Cohort 1 only)



a If suboptimal virologic response is confirmed and the HIV-1 RNA is ≥ 400 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed.
b If genotype/phenotype results are not available by the Week 12 visit, an unscheduled visit should be performed when the laboratory results are available.
c Based on the results of the genotype/phenotype assays, the subject will remain on study drug or study drug will be discontinued at the next scheduled or unscheduled visit, whichever occurs first. If genotyping/phenotyping fails, a repeat specimen will be sent for analysis. If repeat genotyping/phenotyping subsequently fails, study medications can be continued or a new ARV regimen can be configured at the discretion of the investigator, in consultation with the Medical Monitor.
d If no resistance is detected, HIV-1 RNA will be repeated within 3-6 weeks. Investigator reviews and document study drug continuation/discontinuation options. Investigator must discuss with the Medical Monitor prior to study drug discontinuation
e A new ARV regimen will be configured, at the investigator's discretion, and the subject will remain in the study.

6.8.2. Management of Virologic Rebound

Subjects who meet the criteria listed below will be considered to have virologic rebound:

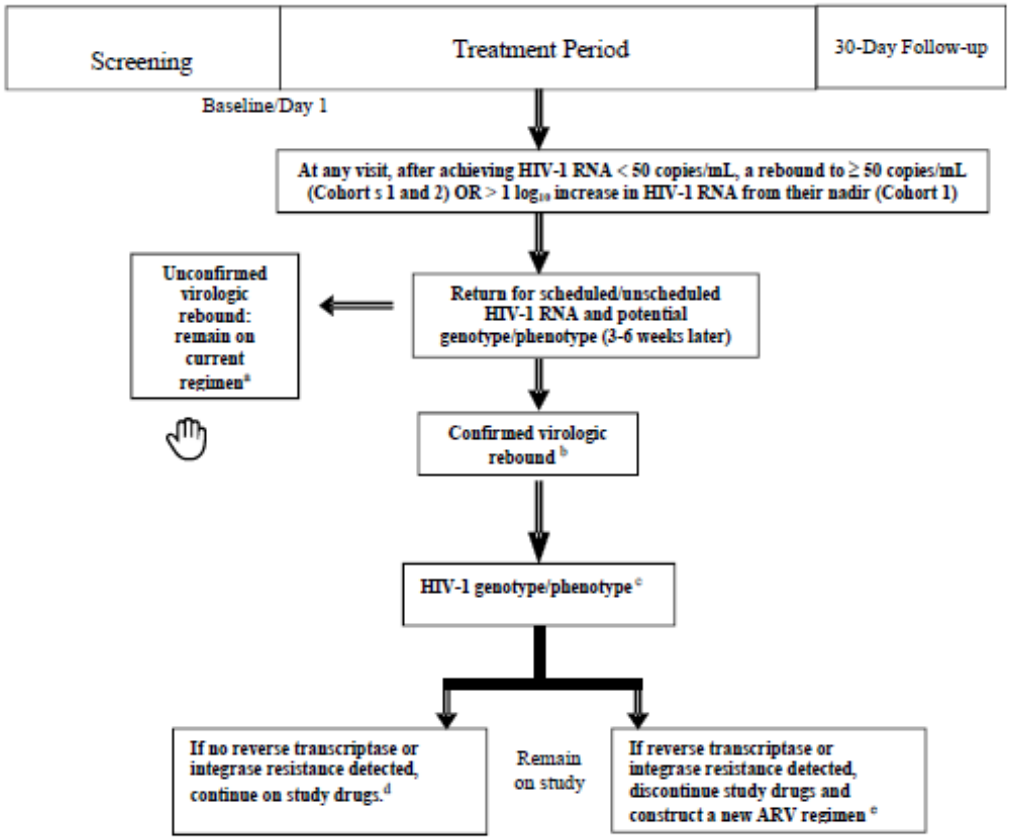
- At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA to
- ≥ 50 copies/mL, which is subsequently confirmed (two consecutive tests) at the following scheduled or Unscheduled visit (3-6 weeks after the date of the original test with HIV-1 RNA to ≥ 50 copies/mL) (Cohorts 1, 2, and 3); OR

- At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed (two consecutive tests) at the following scheduled or Unscheduled visit (3-6 weeks after the date of the original test with HIV-1 RNA to ≥ 50 copies/mL) (Cohort 1 only)

Following the unconfirmed virologic rebound, HIV-1 RNA should be repeated at a scheduled or unscheduled visit (3-6 weeks after the date of the original test with VL ≥ 50 copies/mL). If virologic rebound is confirmed, the samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing if HIV-1 RNA is ≥ 400 copies/mL.

Please refer to Figure 6-2 for the management of subjects who meet the criteria for virologic rebound.

Figure 6-2. Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject will remain on their current regimen.
b If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 400 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase) will be analyzed.
c Based on the results of the genotype/phenotype assays, the subject will remain on study drug or study drug will be discontinued. If genotyping/phenotyping fails, a repeat specimen will be sent for analysis. If repeat genotyping/phenotyping subsequently fails, study medication can be continued or a new ARV regimen can be configured at the discretion of the investigator, in consultation with the Medical Monitor.
d If no resistance is detected. Investigator reviews study drug continuation/discontinuation options and discuss with the Medical Monitor prior to study drug discontinuation
e A new ARV regimen will be configured, at the investigator's discretion, and the subject will remain in the study

6.8.3. Subjects with ≥ 400 copies/mL of HIV-1 in Absence of SVR or VR

Subjects may have an antiviral response that is sustained at ≥ 400 copies/mL but do not meet either SVR or VR criteria. Subjects in that category could have an antiviral response that was

1 $\log_{10}$ HIV-1 RNA reduction from baseline (and therefore did not meet SVR criteria), but did not show > 1 $\log_{10}$ increase from nadir. These subjects will be analyzed for resistance at Week 48 or their last time point on study. Subjects who have achieved HIV-1 RNA < 50 copies/mL could subsequently experience unconfirmed blips ≥ 400 copies/mL of HIV-1 RNA. Such subjects will be analyzed for resistance if the unconfirmed rebound happens at Week 48 or last visit while receiving study drugs (or within 72 hours of discontinuation of study treatment). Subjects with ≥ 400 copies/mL of HIV-1 RNA at study discontinuation (after Week 8) while receiving study drugs (or within 72 hours of discontinuation of study treatment) will be analyzed for resistance.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after Screening (before the administration of study investigational medicinal product).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.
- Complications and termination of pregnancy (see Section 7.4 for additional information)
- All AEs that occur from the Screening visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.4)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history case report form (CRF).
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.2. Assessment of Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded on the AE CRF page. The AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to investigational medicinal product or to a study procedure, the action taken with investigational medicinal product due to the AE, and the severity of the AE. The investigator is responsible for final review and confirmation of accuracy of events, relationship and severity confirmed by the signature on the CRF book. The relationship to investigational medicinal product therapy should be assessed using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol-mandated procedures such as venipuncture or biopsy.

7.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity

- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product

- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

  Examples of such events are as follows:

  — Intensive treatment in an emergency room or at home for allergic bronchospasm

  — Blood dyscrasias or convulsions that do not result in hospitalization

  — Development of drug dependency or drug abuse

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the investigational medicinal product(s).

- The subject may not have been on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 7.3.

7.4. Special Situations

7.4.1. Definitions of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, pregnancy regardless of an associated AE, or overdose.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent, sporadic, or intentional excessive use of a medicinal product by a patient.

Misuse is defined as any use of a medicinal product in a way that the product is intentionally and inappropriately used not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labeling (as it applies to the daily dose for the subject/patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s)

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.4.2. Instructions for Reporting Special Situations

7.4.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies occurring in female subjects that are identified after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the study, including the post-study drug follow-up period, to Gilead Global Patient Safety (GLPS) (formerly Pharmacovigilance and Epidemiology) using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.5 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the adverse event term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to Gilead Sciences.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. If the conclusion of the pregnancy occurs after the post-study drug follow up period, then the outcome should be reported to Gilead GLPS using the Pregnancy Outcome Report form. Gilead GLPS contact information is as follows:

Email: CCI [redacted] and fax: CCI [redacted]

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.4.2.2. Instructions for Reporting Other Special Situations

All other Special Situation reports must be reported on the Special Situations Report Form and forwarded to Gilead GLPS within 24 hours.

These reports must consist of situations that involve study investigational medicinal products (IMPs) and Gilead concomitant medications, but do not apply to non-Gilead concomitant medications (i.e., except for situations that result in adverse events, special situations involving non-Gilead concomitant medications will not be reported). Any inappropriate use of non-protocol approved medications should not be reported as "misuse" but may be more appropriately documented as a protocol deviation if applicable.

Refer to Section 7.5 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

7.5. Serious Adverse Event Reporting Requirements

7.5.1. All Serious Adverse Events

Gilead Sciences is required to expedite to worldwide regulatory authorities reports of SAEs which may be in the form of line listings, Serious Adverse Drug Reactions or Suspected Unexpected Serious Adverse Reactions (SUSARs); therefore, Gilead Sciences (or the CRO on the behalf of Gilead Sciences) must be notified immediately regarding the occurrence of any SAE that occurs after the subject consents to participate in the study, including SAEs resulting from protocol-associated procedures performed from Screening onwards. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form (see following bullet). During the study conduct sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS. Contact information is as follows:

Gilead GLPS:	Fax: E-mail:	PPD PPD
Gilead Sciences Medical Monitor:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.	

For fatal or life-threatening events, also e-mail or fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Transmission of such documents should occur with Personal Subject Details de-identified, without losing the traceability of a document to the Subject Identifiers.

Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF and the event description section of the SAE form.

Follow-up of adverse events will continue through the last day on study (including the follow-up off-study medication period of the study) and/or until the investigator and/or Gilead Sciences determine that the subject's condition is stable. Gilead Sciences may request that certain adverse events be followed until resolution.

Electronic Serious Adverse Event (eSAE) Reporting Process

Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to Gilead GLPS as described above.

As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

7.5.2. Investigator and Sponsor Reporting Requirements for SAEs

An SAE may qualify for reporting to regulatory authorities. Expectedness of SAEs will be determined by Gilead Sciences using reference safety information specified in the Investigator's Brochure.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IRB or IEC as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), the Sponsor or specified designee will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs.

7.5.3. Post-Study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol-required post-treatment follow-up).

Any SAEs and deaths that occur after the post-treatment follow-up visit but within 30 days of the last dose of investigational medical product, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-required post-treatment follow-up; however, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal products, he/she should promptly document and report the event to Gilead GLPS.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1 and 7.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.

Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose upon discussion with the Medical Monitor.

Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.

Any questions regarding toxicity management should be directed to the Medical Monitor.

7.7.1. Management of Changes in Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (GFR), according to the Schwartz formula, will be followed post-baseline during the study. All subjects with estimated GFR < 50 mL/min must have serum creatinine and subject's height and weight measured again within 3 calendar days of receipt of results. If a subject has confirmed estimated GFR < 50 mL/min, the Medical Monitor should be notified and investigational medicinal product discontinued.

7.7.2. Management of Posterior Uveitis Cases

In a nine-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12-18 mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation; this finding did not occur in animals given lower doses and it has not occurred in other animal studies. This pre-clinical finding has also not been observed in humans where the dose is much lower, nor have there been reports of posterior uveitis in human clinical studies.

Across all ongoing Phase 2 and Phase 3 studies in which 2,394 subjects have received E/C/F/TAF STR for up to 96 weeks, eye disorders were uncommon, generally unrelated to treatment, and balanced between treatment arms. None were indicative of posterior uveitis, and none resulted in permanent discontinuation of study drugs. One subject in Study GS-US-292-0106 had an AE of intermediate uveitis that was considered related to study drug by the investigator but resolved while the subject continued on study drug without interruption.

Nonetheless, if any subjects develop signs or symptoms of posterior uveitis, investigators should contact the Gilead Medical Monitor to discuss the need for additional ophthalmologic evaluation including dilated fundoscopy and optical coherence tomography (OCT).

7.7.3. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the investigator.

7.7.4. Grade 3 Laboratory Abnormality or Clinical Event

For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.7.5. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Cohort 1

The primary analysis objectives are:

Part A:

- To evaluate the steady state PK for EVG and TAF and confirm the dose of the E/C/F/TAF STR in HIV-1 infected, 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 analysis objectives 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

Cohort 2

The primary analysis objectives 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 analysis objectives 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

Cohort 3

The primary analysis objectives 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 LD 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 analysis objectives 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, weighing ≥ 14 to < 25 kg

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8.1.2. Primary Endpoints

Cohort 1

In Part A the primary endpoints are PK parameter of AUC_{tau} for EVG and AUC_{last} for TAF and in Part B the primary endpoints include incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

Cohort 2

In Part A the primary endpoints include PK parameter of AUC_{tau} for EVG and AUC_{last} for TAF, and in Part B the primary endpoints include incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

Cohort 3

The primary endpoints include PK parameter of AUC_{tau} for EVG and TAF, incidence of treatment-emergent SAEs, and all treatment-emergent adverse events.

8.1.3. Secondary Endpoints

Cohort 1

For Part A, the secondary endpoints include:

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC, TFV and COBI.

For Part B, the secondary endpoints include:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis
- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) and in CD4+ cell count (cells/μL) and percentage at Weeks 24 and 48

Cohort 2

For Part A, the secondary endpoints include:

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC, TFV and COBI.

For Part B, the secondary endpoints include:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis
- The change from baseline in CD4+ cell count (cells/μL) and percentage at Weeks 24 and 48

Cohort 3

The secondary endpoints include:

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau}, for FTC, TFV and COBI.
- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis.
- The change from baseline in CD4+ cell count (cells/μL) and percentage at Weeks 24 and 48

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set

The full analysis set will include all subjects who received at least one dose of study drug.

8.2.1.2. Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of study drug.

All the data collected up to 30 days after subjects permanently discontinue their study regimen will be included in the safety summaries.

8.2.1.3. BMD Analysis Sets

8.2.1.3.1. Spine BMD Analysis Set

The spine BMD analysis set will include all subjects who received at least one dose of study drug, had nonmissing spine BMD value for the Baseline visit and at least one postbaseline visit.

8.2.1.3.2. Total Body Analysis Set

The total body less head BMD analysis set will include all subjects who received at least one dose of study drug, had nonmissing total body less head BMD value for the Baseline visit and at least one postbaseline visit.

8.2.1.4. Pharmacokinetics (PK) Analysis Sets

8.2.1.4.1. Intensive PK Analysis Set

The Intensive PK analysis set will include all subjects who received at least one dose of study drug and for whom steady-state pharmacokinetic profiles at Intensive PK visit are evaluable. The Intensive PK analysis set will be used for detailed PK analysis of EVG, COBI, FTC, TAF, and TFV by cohort.

8.2.1.4.2. PK Analysis Set

The PK analysis set will include all subjects who received at least one dose of study drug and for whom at least one observed concentration data of any analyte of interest is available. The PK analysis set will be used for analysis of general PK and trough blood concentrations by cohort.

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8.2.2. Data Handling Conventions

Natural logarithm transformation for key PK parameters, such as C_{max}, C_{tau} and AUC_{tau}, will be applied for pharmacokinetic analysis.

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age.

Baseline data including body weight, height, body mass index, HIV-1 infection, and enrollment distribution will be summarized.

8.4. Efficacy Analysis

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 (Windows: Study Days 140-195) as defined by the FDA-defined snapshot algorithms are described below.

Virologic outcome at Week 24 for the Cohort 1 (treatment-naïve) subjects will be defined into the following 3 categories:

- HIV-1 RNA < 50 copies/mL: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 24 analysis window;
- HIV-1 RNA ≥ 50 copies/mL: this includes subjects who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window, or who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and who discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or who 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 Analysis Window: this includes subjects who do not have on-treatment HIV-1 RNA at Week 24 window because of the following:
  - Discontinuation of study drug prior to or in the Week 24 analysis window due to AE or death; 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 in the Week 24 window but on study drug

Virologic outcome at Week 24 for the Cohort 2 and Cohort 3 (treatment suppressed) subjects will be defined similarly with the exception of classifying subjects who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL into the "HIV-1 RNA ≥ 50 copies/mL" category.

Virologic outcomes will be summarized using frequency counts and percentages based on the Full analysis set.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (Windows: Study Days 308-377) and the percentage of subjects with HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 will be summarized in the same manner as described above.

The changes from baseline in plasma $\log_{10}$ HIV-1 RNA (Cohort 1 only) and in CD4+ cell count will be summarized using descriptive statistics.

8.5. Safety Analysis

All safety analyses will be performed using the safety analysis set.

8.5.1. Extent of Exposure

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study regimen, inclusive, regardless of temporary interruptions in study regimen administration.

Dosing information for individual subjects will be listed.

8.5.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Adverse events meeting the following criteria are defined as treatment-emergent AEs.

1) Any AEs with onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

2) Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided. Additional summaries will include summaries for adverse events by grade, investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.5.3. Laboratory Evaluations

Laboratory results will be expressed both in the original measurement and in terms of the toxicity grade according to toxicity grading table attached in Appendix 4. Changes from baseline in quantitative laboratory tests will be summarized by visit (including eGFR estimated by cystatin C clearance for Cohorts 1 and 2). Cystatin C will not be collected for Cohort 3. The maximum toxicity grade will be summarized by laboratory parameter. The post-baseline laboratory measurements obtained up to 30 days after the last dose date of the study drug will be included in the quantitative and qualitative summaries.

8.5.4. Bone Safety

Selected bone safety, including:

Cohorts 1 and 2: serum bicarbonate, N-telopeptide, C-telopeptide, osteocalcin, procollagen type 1 N-terminal propeptide (P1NP), and urine bicarbonate and N-telopeptide

For all cohorts: bone specific alkaline phosphatase, PTH, 25OH Vitamin D, and 1,25OH Vitamin D

All the above will be summarized by visit using descriptive statistics.

8.5.5. Renal Safety

Selected renal safety, including urine chemistry, retinol binding protein, and beta-2-microglobulin, will be summarized by visit using descriptive statistics.

8.5.6. Spine and Total Body Less Head Bone Mineral Density

For all cohorts, the percentage change from baseline in spine and total body less head BMD will be summarized by study visit. BMD z-score will be derived for each BMD measurement if the corresponding reference population is available. Z-scores for spine and total body less head BMD and change from baseline in z-scores will also be summarized by visit.

8.5.7. Tanner Stage Assessment

The Tanner stage score will be summarized by study visit.

8.5.8. Palatability

Palatability will be summarized using descriptive statistics by cohort.

8.5.9. Acceptability

Acceptability will be summarized using descriptive statistics.

8.6. Pharmacokinetic Analysis

The concentration data of EVG, COBI, FTC, TAF, and TFV over sampling time will be listed and summarized. Pharmacokinetic parameters (e.g., AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, apparent CL, apparent V_z and $T_{½}$) will be listed and summarized for analytes EVG, COBI, FTC, TAF, and TFV using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation %, standard deviation, median, Q1, Q3, minimum, and maximum).

To determine whether the adult dose of TAF in adolescents (Cohort 1) and children (Cohort 2 and 3), respectively, achieves similar TAF systemic exposures to that in adults, an analysis of variance will be carried out for log-transformed AUC as a primary parameter while other pharmacokinetic parameters such as C_{max} will be explored. TAF data from the current study will be compared to the integrated historical control data using pharmacokinetic equivalence testing with an equivalency boundary of 70% to 143% for the 90% confidence interval. In addition, the 95% confidence interval of the geometric mean estimate of apparent CL and V_z of TAF will be provided.

Similar analysis will be done for log-transformed AUC_{tau} as a primary parameter to determine whether the adult dose of EVG in adolescents and children, respectively, achieves similar EVG systemic exposures to that in adults. Other pharmacokinetic parameters such as C_{max} and C_{tau} will be explored. EVG data from the current study will be compared to the integrated historical control data using pharmacokinetic equivalence testing with an equivalency boundary of 70% to 143% for the 90% confidence interval. The 95% confidence interval of the geometric mean estimate of apparent CL and V_z of EVG will also be provided.

Pharmacokinetic parameters of COBI, FTC, and TFV will be summarized using descriptive statistics.

8.7. Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will review the progress, efficacy, and safety data of this study while the study is ongoing. No formal stopping rules will be used by the IDMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse events associated with a study regimen warrant the early termination of the study in the best interest of the participants. A separate IDMC charter will be finalized prior to initiation of dosing.

8.8. Analysis Schedule

Cohort 1

A PK analysis will be performed after the first 18 subjects (regardless of age distribution) complete the Intensive PK portion of the study (Part A). With confirmation of TAF exposure from the first 18 subjects, screening in Part B will be initiated. If more than 18 subjects are enrolled in Part A, the final PK analysis will be performed after all subjects complete the Intensive PK portion of the study. The Week 24 analysis of efficacy and safety will be conducted after the last subject completes 24 weeks on study. The Week 48 analysis of efficacy and safety will be conducted after the last subject completes 48 weeks on study.

Cohort 2

A PK analysis will be performed after all subjects complete the Intensive PK portion of the study (Part A). The Week 24 analysis of efficacy and safety will be conducted after the last Part A subject completes 24 weeks on study and also after all subjects complete 24 weeks on study. The Week 48 analysis of efficacy and safety will be conducted after the last subject completes 48 weeks on study.

Cohort 3

A PK analysis will be performed after all subjects complete the Intensive PK portion of the study. The Week 24 analysis of efficacy and safety will be conducted after all subjects complete 24 weeks on study. The Week 48 analysis of efficacy and safety may be conducted after the last subject completes 48 weeks on study.

8.9. Sample Size and Power

Cohorts 1 and 2

A minimum of 18 Part A subjects from each cohort will receive E/C/F/TAF STR in this study. PK data from these subjects will have 92% power to conclude exposure equivalence of TAF AUC_{last} in adolescents and children, respectively vs. 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-subject standard deviation (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 subjects from each cohort will also provide > 99% power to target a 95% confidence interval 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 subjects (subjects from Part A and subjects 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 amendment 2 of the study protocol was finalized, the adult data included in Genvoya label have become available and will be used as historical control for comparison for Cohort 2 (ie, intensive PK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK 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 subjects 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 intersubject standard deviation (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 subjects will also provide > 86% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of CL and V_z of TAF respectively, assuming a CV of 53% for CL and 76% for V_z (based on population PK data from Studies GS-US-292-0104 and GS-US-292-0111 combined).

Cohort 3

Twenty-five evaluable subjects 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 ratios is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level of 0.05, and the intersubject standard deviations (natural log scale) of EVG AUC_{tau} and TAF AUC_{tau} are 0.34 ng•hr/mL and 0.52 ng•hr/mL. For historical adult data, we used intensive PK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK data from Studies GS-US-292-0104 and GS-US-292-0111 combined for TAF AUC_{tau}.

Twenty-five evaluable subjects will also provide > 99% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of apparent CL and V_z of TAF respectively, assuming the standard deviation in natural log scale is 0.51 for CL and 0.54 for V_z (based on population PK 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.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, Washington, Seoul, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, "Protection of Human Subjects", and 21 CFR, part 56, "Institutional Review Boards", are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify Gilead Sciences of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/EC/REB. Approval from the IRB/EC/REB must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB/EC/REB approval must also be submitted to the IRB/EC/REB for approval before implementation.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/EC/REB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB/EC/REB, or laboratory. The investigator must keep a Screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/EC/REB approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include, but is not limited to sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);

- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify

Gilead Sciences before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead Sciences must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

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9.1.6. Electronic Case Report Forms (eCRFs)

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture system unless otherwise directed. This also applies to records for those subjects who fail to complete the study (even during a prerandomization screening period if an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the electronic data capture system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the electronic data capture system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other timepoints (as instructed by Gilead), the investigator should apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug kits. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug kits dispensed to subjects must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits
- The date, subject number, and the study drug kit number dispensed.
- The date, quantity of used and unused study drug kits returned, along with the initials of the person recording the information.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. While performing drug accountability at an on-site monitoring visit is preferred, remote drug accountability can be performed with prior Gilead approval.

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRB/EC/REBs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB/EC/REB in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).

Gilead Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead Sciences, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met***:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead Sciences in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 9.1.4).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at Investigator Meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Airoldi M, Zaccarelli M, Bisi L, Bini T, Antinori A, Mussini C, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. Patient preference and adherence 2010;4:115-25.

Bangsberg DR, Ragland K, Monk A, Deeks SG. A one-pill, once-daily, fixed-dose combination (FDC) of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (EFV/FTC/TDF) regimen is associated with higher unannounced pill count adherence than non-one pill, once-daily [Poster]. 17th Conference on Retroviruses and Opportunistic Infections (CROI); 2010 February 16-19; San Francisco, CA.

Capeau J. Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. Clin Infect Dis 2011;53 (11):1127-9.

Dejesus E, Young B, Morales-Ramirez JO, Sloan L, Ward DJ, Flaherty JF, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr 2009;51 (2):163-74.

Department of Health and Human Services (DHHS), Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at https://aidsinfo.nih.gov/guidelines. [Report] Last Updated: May 22. 2018.

EMTRIVA®, Gilead Sciences Inc. EMTRIVA® (emtricitabine) capsule, for oral use. EMTRIVA® (emtricitabine) oral solution. US Prescribing Information. Foster City, CA. Revised November. 2012:

Gilead Sciences Inc. VIREAD® (tenofovir disoproxil fumarate) Tablets and Powder for oral use. US Prescribing Information. Foster City, CA. Revised August 2012:

Hodder SL, Mounzer K, Dejesus E, Ebrahimi R, Grimm K, Esker S, et al. Patient-Reported Outcomes in Virologically Suppressed, HIV-1-Infected Subjects After Switching to a Simplified, Single-Tablet Regimen of Efavirenz, Emtricitabine, and Tenofovir DF. AIDS Patient Care STDS 2010;24 (2):87-96.

Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf . 2016.

Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352 (9142):1725-30.

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining Morbidity and Mortality Among Patients With Advanced Human Immunodeficiency Virus Infection. N Eng J Med 1998;338 (13):853-60.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1–239. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed August 22. 2012.

Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection: Available at: http://aidsinfo.nih.gov/ContentFiles/PediactricGuidelines.pdf. Accessed September 9, 2012. 2011:1-279.

Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006-2009. PLoS ONE 2011;6 (8):e17502.

Sax PE, Meyers J, Mugavero M, Davis KL. Adherence to Antiretroviral Treatment Regimens and Correlation with Risk of Hospitalization Among Commercially Insured HIV Patients in the United States [Poster O113]. 10th International Congress on Drug Therapy in HIV Infection; 2010 November 7-11; Glasgow, UK.

Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015;385:2606-15.

Sterne J, Hernán M, Ledergerber B, Tilling K, Weber R, Sendi P, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005;366 (9483):378-84.

World Health Organization (WHO). Developing Dosing Guidance For New And Upcoming Formulations Of Paediatric Antiretrovirals In Line With Treatment 2.0 Priorities. Presented at: Paediatric Antiretroviral Working Group.; 2011 25-26 October; Geneva, Switzerland.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-292-0106, Amendment 7, 01 June 2021

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
PPD

DocuSigned by:
PPD
GILEAD
Signed By: PPD
Signing Reason: I approve this document
Signing Time: 2021-06-02 13:28:11Z (UTC)
O: Gilead Sciences Inc., OU: Gilead Sciences Inc.
L: Foster City, C: US
Issuer: Symantec Individual Document Signing RSA CA
PPD

Signature

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

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]	Cohorts 1 and 2 Post-Week 240; Cohort 3 Post-Week 96 Every 24 weeks	30-Day Follow-up[d]	ESDD[e]
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	X
Concomitant Medications	X	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	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	X	
Height	X	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	X
Tanner Stage Evaluations[h]		X								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	X
Chemistry Profile[k]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Full flow cytometry panel testing	X	X		X		X	X	X	X	X	X	X	X	X	X[ii]	X	X
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	X
Plasma Storage Sample[n]		X[ee]				X[z]	X	X	X	X	X[ee]	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]	Cohorts 1 and 2 Post-Week 240; Cohort 3 Post-Week 96 Every 24 weeks	30-Day Follow-up[d]	ESDD[e]
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	X
Estimated Glomerular Filtration Rate[o]	X	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	X
Dispense Dosing Diary (for Part A subjects, inclusive of Cohort 3)			X[ff]	X													
Review Dosing Diary (For Part A subjects, inclusive of Cohort 3)					X												
Single PK Sampling[r]						X[z]	X	X	X		X[dd]	X[dd]					X
Trough PK Sample[s]			X[cc]	X[ee]		X[ff]				X			X				
Intensive PK Sampling[t]					X												
CCI																	
DXA Scan (Lumbar spine & Total Body)[v]		X								X			X	X	X[ij]		
Bone Safety[w]	X[ff]	X[ee]					X[dd]	X		X			X	X	X[kk]		
Urine Renal Safety[x]	X[ff]	X[ee]					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]	Cohorts 1 and 2 Post-Week 240; Cohort 3 Post-Week 96 Every 24 weeks	30-Day Follow-up[d]	ESDD[e]
Study Drug Dispensation		X				X	X	X	X	X	X	X	X	X	X		
In-clinic Dosing[y]		X	X	X		X		X		X			X				
Drug Accountability[hh]			X	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 subjects 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 subjects 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 subject 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 subject 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 subjects not enrolling in the extension phase of the study or those subjects 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 subjects ≥ 6 years of age and no longer be performed once a subject 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. CCI [redacted]

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 subjects (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 subjects, back-up samples will be collected at all visits.

[redacted]

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

[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 (Part B subjects only) and Week 12 between 0.25-4 hours post-dose. A random PK sample collected at Week 8, Week 16, and Week 32. Cohort 2: a timed PK at Week 12 between 0.25-4 hours post-dose. A random PK samples at Week 8 and Week 16. Cohort 3: a timed PK sample collected between 0.25 and 4 hours post-dose at Week 8, 12, and 16.

s Subjects must come into the clinic without taking their dose of E/C/F/TAF STR and subjects 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 subjects in Cohorts 1 and 2 and Week 48 for Cohort 1 only. For subjects in Cohort 3, a trough sample will be collected at Weeks 4 and 24.

t Part A subjects 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 subject 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 subject 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 subject 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 CCI manual for sample collection and processing details.

[redacted]

v DXA scans to be performed in all eligible subjects 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
For all cohorts, bone safety including:
Serum: bone specific alkaline phosphatase, parathyroid hormone (PTH), 25OH Vitamin D and 1, 25OH Vitamin D

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

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

z Cohort 1 Part B subjects only

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

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

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

dd Cohort 1 subjects only

ee Cohorts 1 and 2 subjects only

ff Cohort 3 subjects

CCI [redacted]

hh Performing drug accountability at an on-site monitoring visit is preferred. Gilead prior approval to perform remote drug accountability is required.

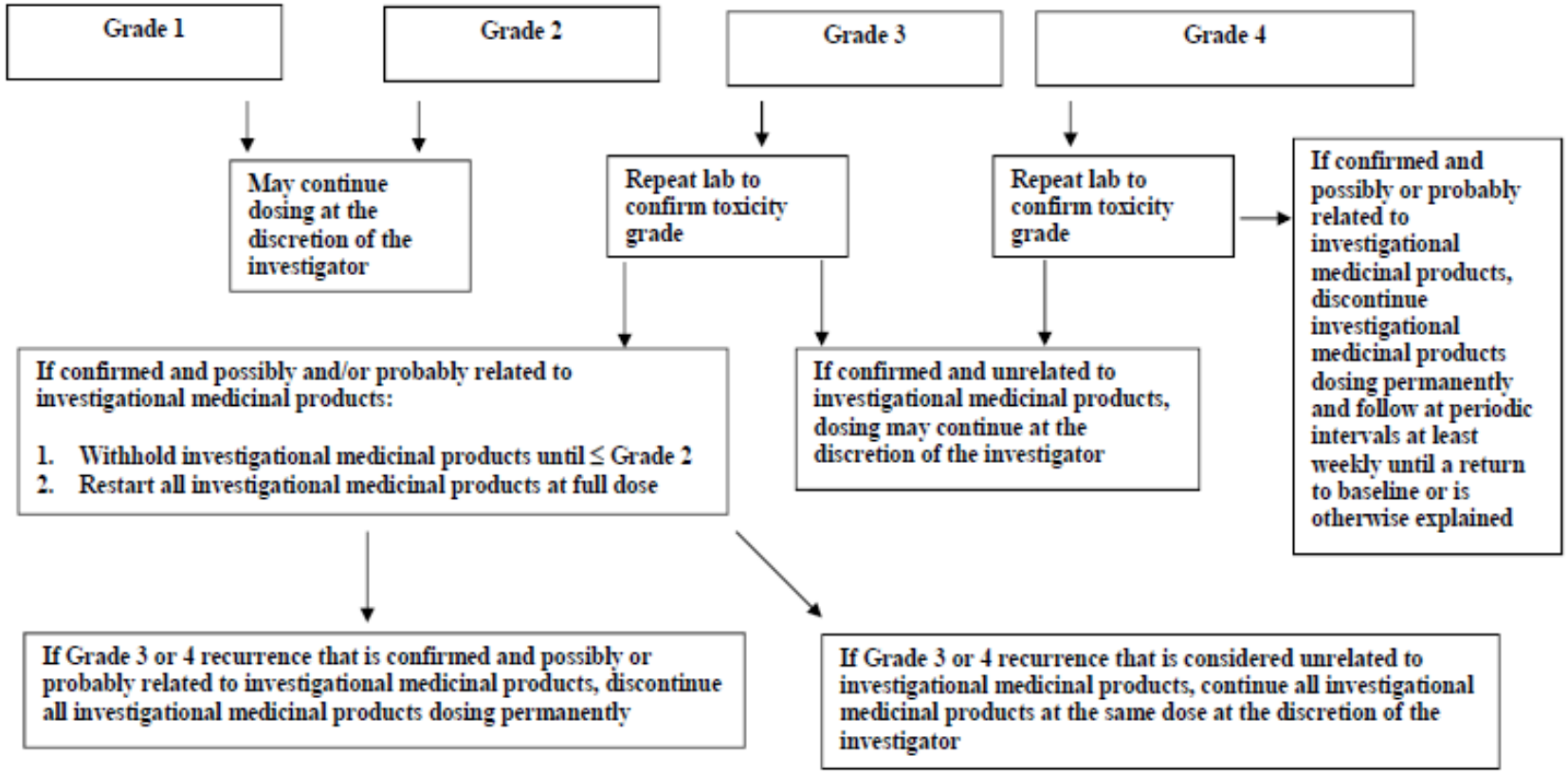
ii CD4 cell count and percentage only will be performed every 24 weeks for Cohorts 1 and 2 CCI [redacted]

[redacted]

CCI [redacted]:

CCI [redacted]

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Infant, **2 – ≤ 7 Days**	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, **1 Day**	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	40 to 50 µg/mL 40 to 50 mg/L	50 to 60 µg/mL 50 to 60 mg/L	60 µg/mL 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	159 mEq/L 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	7.0 mEq/L 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days Infant, < 7 Days**	 7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	 7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	 6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	 < 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	 >ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	 > 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL 3.10 to 3.23 mmol/L	 > 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL 3.23 to 3.38 mmol/L	 > 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	ULN to 6.0 mg/dL ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	7.0 mg/dL 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL 513 µmol/L > 25.0 mg/dL 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	190 mg/dL >4.92 mmol/L 190 mg/dL >4.92 mmol/L	NA NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	300 mg/dL 7.77 mmol/L 300 mg/dL 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females Males	 >ULN - 10 RBC/HPF 6-10 RBC/HPF	 > 10-75 RBC/HPF > 10-75 RBC/HPF	 75 RBC/HPF 75 RBC/HPF	 NA NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years** **Pediatric > 3 Mo to < 10 Years**	 200 to 999 mg/24 h 201 to 499 mg/m^2/24 h	 >999 to 1999 mg/24 h >499 to 799 mg/m^2/24 h	 >1999 to 3500 mg/24 h >799 to 1000 mg/m^2/24 h	 > 3500 mg/24 h > 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:
Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	159–179 mmHg systolic OR 99–109 mmHg diastolic	179 mmHg systolic OR 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life- threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak- ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of E/C/F/TAF STR have demonstrated that a clinically relevant interaction with contraceptive steroids was observed or suspected. If used, a hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol. In addition, non-clinical toxicity studies of E/C/F/TAF STR have demonstrated no adverse effect on fertility or embryo-fetal development. However, there is no clinical data of E/C/F/TAF STR in pregnant women. Please refer to the latest version of the Investigator's Brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following Screening until the last dose of study drug.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure® micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)
  - Hormonal methods (including Intrauterine hormone-releasing system (IUS)) must be used with barrier methods described above. The hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the last study drug dose.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential. Male subjects must also refrain from sperm donation during treatment and until at least the end of the protocol-defined posttreatment period.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.1.

Appendix 6. Stage-3-Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent* Candidiasis of bronchi, trachea, or lungs Candidiasis of esophagus

Cervical cancer, invasive†

Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month Cytomegalovirus retinitis (with loss of vision)

Encephalopathy attributed to HIV§

Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)

Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (>1 month's duration) Kaposi sarcoma

Lymphoma, Burkitt (or equivalent term) Lymphoma, immunoblastic (or equivalent term) Lymphoma, primary, of brain

Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary *Mycobacterium tuberculosis* of any site, pulmonary†, disseminated, or extrapulmonary *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary *Pneumocystis jirovecii* (previously known as "*Pneumocystis carinii*") pneumonia

Pneumonia, recurrent†

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent Toxoplasmosis of brain, onset at age >1 month

Wasting syndrome attributed to HIV§

* Only among children aged <6 years.
† Only among adults, adolescents, and children aged ≥6 years.
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: CDC. 1994 Revised classificationsystem for human immunodeficiency virus infection in children less than 13 years of age.
MMWR 1994;43(No. RR-12). CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(No. RR-17).

Appendix 7. Tanner Stages

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (prepubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.