STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis
Name of Test Drugs:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination Bictegravir/Emtricitabine/Tenofovir alafenamide (B/F/TAF) Fixed-Dose Combination
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
B/F/TAF	bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg fixed-dose combination, Biktarvy®
BMI	body mass index
BLQ	below the limit of quantitation
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CI	confidence interval
COBI	cobicistat (Tybost®)
CPK	creatine phosphokinase
CRF	case report form
CV	coefficient of variation
E/C/F/TAF	single-tablet regimen of elvitegravir (EVG) 150 mg/ cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg/ tenofovir alafenamide (TAF) 10mg; coformulated; Genvoya®
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault formula
ESDD	early study drug discontinuation
ESRD	end stage renal disease
EVG	elvitegravir
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine (Emtriva®)
GFR	glomerular filtration rate
GSI	Gilead Sciences, Inc.
HD	hemodialysis
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus (type 1)
HLGT	high level group terms
HLT	high level term

IDMC	independent data monitoring committee
INR	international normalized ratio of prothrombin time
LOCF	last observation carried forward
LDL	low-density lipoprotein
LLT	lowest level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
OL	open label
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
PT	preferred term
PTH	parathyroid hormone
Q	quartile
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatinine concentration
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated; Stribild®
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TEAE	Treatment-emergent adverse event
TFL	tables, figures, and listings
TFV	tenofovir
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis for Study GS-US-292-1825, which will be performed when all subjects have completed the study or prematurely discontinued from the study. This SAP is based on the study Protocol Amendment 2.1, dated 01 May 2018, and electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made to the analyses after the finalization of the SAP will be documented in the final clinical study report. Analyses that were performed as part of interim clinical study reports will not be repeated for the final analysis unless otherwise specified.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF; E/C/F/TAF) fixed-dose combination (FDC) in HIV-1 infected adults with end stage renal disease (ESRD) on chronic hemodialysis (HD) at Week 48

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC in HIV-1 infected adults with ESRD on chronic HD at Week 96

- To evaluate the proportion of subjects receiving E/C/F/TAF FDC achieving virologic response (HIV-1 RNA < 50 copies/mL, as defined by the FDA snapshot analysis) at Weeks 24, 48, and 96

- To evaluate plasma pharmacokinetics (PK) of EVG, COBI, FTC, TAF, and tenofovir (TFV) in HIV-1 infected patients with ESRD on chronic HD

- To evaluate the safety and tolerability of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) FDC in HIV-1 infected adults with ESRD on chronic HD in the open-label extension phase

1.2. Study Design

Design Configuration and Subject Population

GS-US-292-1825 is an open-label, multicenter, single-arm study to assess the safety, tolerability, PK, and efficacy of the E/C/F/TAF FDC dosed once daily in HIV-infected adult subjects with ESRD on chronic HD.

All subjects will switch from their current antiretroviral (ARV) regimen to E/C/F/TAF on Day 1. The treatment duration for E/C/F/TAF will be at least 96 weeks.

After Week 96, subjects in the US will continue to take their study drug and attend visits every 12 weeks until the End of E/C/F/TAF visit. At Week 96 or the End of E/C/F/TAF Visit, subjects will discontinue E/C/F/TAF FDC and be given the option to receive open-label (OL) B/F/TAF FDC. All subjects participating in the OL extension of B/F/TAF FDC will return for study visits at B/F/TAF Week 4 OL, Week 12 OL, and every 12 weeks thereafter for at least 48 weeks.

Subjects who do not wish to participate in the B/F/TAF OL extension phase will discontinue study drug at Week 96.

Approximately 50 subjects with ESRD on chronic HD will be enrolled.

Treatment Groups

All enrolled subjects will receive the following treatment:

- FDC of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg administered orally, once daily with food until the next hemodialysis. On the day of hemodialysis, study drug should be administered after completion of hemodialysis.

Subjects who enroll into the B/F/TAF OL extension phase will receive the following treatment:

- FDC of bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg administered orally, once daily without regard to food until the next hemodialysis. On the day of hemodialysis, study drug should be administered after completion of hemodialysis.

Key Eligibility Criteria

HIV-infected adults who meet the following criteria:

- No documented history of HIV-1 resistance to EVG, FTC, lamivudine (3TC), or TFV
- Currently receiving a stable ARV regimen for ≥ 6 consecutive months prior to screening
- Plasma HIV-1 RNA < 50 copies/mL for at least 6 months preceding the screening visit
- CD4 cell count of ≥ 200 cells/μL
- ESRD with eGFR < 15 mL/min by Cockcroft-Gault (CG)
- On chronic HD for ≥ 6 months prior to screening
- Hepatitis C virus (HCV) infection allowed
- Hepatitis B virus (HBV) infection not allowed

Study Periods / Phases

The study will consist of a 30-day screening period (within 30 days before Day 1 visit), followed by a 96-week E/C/F/TAF treatment period.

After Week 96, all subjects participating in the B/F/TAF OL extension phase will receive B/F/TAF FDC for at least 48 weeks.

End of the study will occur when the last subject enrolled in the study has completed their last observation (or visit).

After a subject has completed/terminated their participation in the study, long-term care of the subject will remain the responsibility of their primary treating physician.

Schedule of Assessments (E/C/F/TAF Phase)

Following Screening, eligible subjects will be required to return for study visits at Day 1 and Weeks 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96. After the Week 96 visit, subjects who are not planning to participate in the B/F/TAF OL extension phase will stop study drug and complete a 30-day Follow-up visit to complete their participation in the study. Subjects who plan to participate in the B/F/TAF OL extension phase will continue to take E/C/F/TAF and attend visits every 12 weeks until the End of E/C/F/TAF visit.

For all subjects, HBV and HCV serologies will be analyzed at Screening. Adverse events (AEs), concomitant medications, complete or symptom-directed physical examinations, laboratory analyses (hematology and chemistry), HIV-1 RNA, and CD4 cell count will be assessed at Screening, Day 1, and all subsequent study visits. eGFR will be assessed at Screening, Day 1, and all subsequent study visits except the 30-day Follow-up visit. Fasting lipids and glucose will be assessed at Day 1 and every 24 weeks thereafter until Week 96 or End of E/C/F/TAF visit.

Predose whole blood draw for plasma and peripheral blood mononuclear cell (PBMC) samples will be collected from all subjects at Week 4 or Week 12, which must be the day of hemodialysis.

CCI [redacted]

Schedule of Assessments (B/F/TAF OL Extension Phase)

All subjects participating in the B/F/TAF OL extension phase will return for study visits at B/F/TAF Week 4 OL, Week 12 OL, and every 12 weeks thereafter for at least 48 weeks.

Adverse events, concomitant medications, complete or symptom-directed physical examinations, laboratory analyses (hematology and chemistry), HIV-1 RNA, and CD4 cell count will be assessed at each visit. eGFR will be assessed at each visit except the 30-day Follow-up visit. Fasting lipids and glucose will be assessed every 24 weeks.

Site and Stratum Enrollment Limits

Approximately 25 study sites in North America and Europe will participate. There is no enrollment limit for individual sites.

1.3. Sample Size and Power

A sample size of approximately 50 subjects is based on practical considerations and is considered to be sufficient to evaluate the primary objective of this study. The primary endpoint is the incidence of treatment-emergent Grade 3 or higher AEs up to Week 48. The Grade 3 or higher AE rate in Study GS-US-292-0112 in subjects that had mild to moderate renal impairment was 8.8% at Week 48 for the E/C/F/TAF arm. Therefore, with 50 subjects, and an assumed rate of Grade 3 or higher AEs being 10%, this study would provide 95% confidence for the primary endpoint to be within (1.7%, 18.3%) assuming normal approximation to binomial proportions.

CCI [redacted]

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

The Week 12 Independent Data Monitoring Committee (IDMC) analysis was conducted after the first 25 subjects enrolled completed their Week 12 visit of the study or prematurely discontinued the study drug. The IDMC's role and responsibilities and the scope of analysis provided to the IDMC were provided in a mutually agreed upon charter, which defines the IDMC membership, meeting logistics, and meeting frequency.

2.2. Week 24 Analysis

A Week 24 analysis was conducted after all subjects enrolled either completed their Week 24 visit of the study or prematurely discontinued study drug.

2.3. Week 48 Analysis

A Week 48 analysis was conducted after all subjects enrolled either completed their Week 48 visit of the study or prematurely discontinued study drug.

2.4. Week 96 Analysis

A Week 96 analysis was conducted after all subjects enrolled either completed their Week 96 visit of the study or prematurely discontinued from the study.

2.5. Final Analysis

The final statistical analysis will be conducted after all subjects either complete the study or prematurely discontinue from the study.

This SAP describes the analysis plan for the final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final analysis will include all data collected from the E/C/F/TAF and the B/F/TAF OL extension phases of the study. Separate tables and figures will be created for each phase unless otherwise specified. Data collected from both phases will be included in data listings. Data included in each phase are defined as follows:

E/C/F/TAF Phase Data

- For subjects who are never treated in the B/F/TAF OL extension phase of the study, all available data are considered as the E/C/F/TAF phase data.
- For subjects treated in the B/F/TAF OL extension phase of the study, E/C/F/TAF phase data are defined as data collected **up to** the B/F/TAF OL extension phase first dose date except for data on adverse events (AEs), concomitant medications, pregnancy, and death. For AEs, concomitant medications, pregnancy, and death, only data collected **prior to** the B/F/TAF OL extension phase first dose date are included.

B/F/TAF OL Extension Phase Data

- B/F/TAF OL extension phase data are only available from subjects who enter the B/F/TAF OL extension phase of the study. B/F/TAF OL extension phase data are defined as data collected **after** the B/F/TAF OL extension phase first dose date except for data on AEs, concomitant medications, pregnancy, and death. For AEs, concomitant medications, pregnancy, and death, data collected **on or after** the extension phase first dose date are included.

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

By-subject listings will be presented for all subjects in the All Enrolled Subjects Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject.

In general, age (in years) on the date of the first dose of E/C/F/TAF study drug will be used for analyses and presentation in listings. For screen failures, age on the date the informed consent was signed will be used. If only birth year is collected on the eCRF, “01 January” will be used for the unknown birth day and month for the purpose of age calculation; similarly, if only birth year and month are collected on the eCRF, “01” will be used for the unknown birth day for the purpose of age calculation.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completion of study drug.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before data finalization and will be identified in a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided.

3.1.1. All Enrolled Subjects Analysis Set

The **All Enrolled Subjects Analysis Set** will include all subjects who are enrolled into the study. This is the primary analysis set for by-subject listings.

3.1.2. B/F/TAF Enrolled Subjects Analysis Set

The **B/F/TAF Enrolled Subjects Analysis Set** will include all subjects who enrolled into the B/F/TAF OL extension phase of the study. This is the analysis set for by-subject listings that pertain to the B/F/TAF OL extension phase only.

3.1.3. E/C/F/TAF Full Analysis Set

The **E/C/F/TAF Full Analysis Set (FAS)** will include all subjects who (1) were enrolled in the study and (2) received at least 1 dose of E/C/F/TAF study drug. This is the primary analysis set for the E/C/F/TAF efficacy analyses.

3.1.4. B/F/TAF Full Analysis Set

The **B/F/TAF Full Analysis Set (FAS)** will include all subjects who (1) were enrolled in the study and (2) received at least 1 dose of B/F/TAF study drug. This is the primary analysis set for the B/F/TAF efficacy analyses.

3.1.5. E/C/F/TAF Safety Analysis Set

The **E/C/F/TAF Safety Analysis Set** will include all subjects who received at least 1 dose of E/C/F/TAF study drug. This is the primary analysis set for the E/C/F/TAF safety analyses.

3.1.6. B/F/TAF Safety Analysis Set

The **B/F/TAF Safety Analysis Set** will include all subjects who received at least 1 dose of B/F/TAF study drug. This is the primary analysis set for the B/F/TAF safety analyses.

3.1.7. B/F/TAF Plasma PK Analysis Set

The **B/F/TAF Plasma PK Analysis Set** will include all subjects who (1) were enrolled into the study, (2) received at least 1 dose of B/F/TAF study drug, and (3) have at least 1 nonmissing plasma PK concentration value for any analyte of interest reported by the PK lab. The B/F/TAF Plasma PK Analysis Set will be used for general B/F/TAF plasma PK analyses.

3.2. Subject Grouping

For all analyses, subjects will be grouped by treatment received. All subjects received E/C/F/TAF. Subjects who enrolled into the B/F/TAF OL extension phase also received B/F/TAF.

Subjects will be grouped under "GEN" for the E/C/F/TAF phase and under "GEN to OL B/F/TAF" for the B/F/TAF OL extension phase. In the subject listings, subjects who received only E/C/F/TAF will have treatment group of "GEN" and subjects who received E/C/F/TAF and OL B/F/TAF will have treatment group of "GEN to OL B/F/TAF".

3.3. Strata and Covariates

This study did not use a stratified randomization schedule when enrolling subjects. No covariates will be included in efficacy or safety analyses.

3.4. Examination of Subject Subgroups

No subgroup analyses are planned.

3.5. Multiple Comparisons

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window but data were not collected or were unusable
- A visit not occurring in the window
- A subject permanently discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

For missing last dose date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 8.3.5.2, and for concomitant medication in Section 8.6.2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

Laboratory data that are continuous in nature but less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation will be imputed as follows:

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

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

- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

Logarithm (base 10) transformation will be applied to HIV-1 RNA data for efficacy analyses. HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA detected" will be imputed as 19 copies/mL for analysis purposes.

3.8. Analysis Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the day when the first dose of E/C/F/TAF study drug was taken, as recorded on the Study Drug Administration eCRF form.

B/F/TAF Study Day 1 is defined as the day when the first dose of B/F/TAF study drug was taken, as recorded on the Study Drug Administration eCRF form.

Study Days are calculated relative to Study Day 1 and B/F/TAF Study Day 1. For events that occurred on or after Study Day 1, study days are calculated as (visit date minus Study Day 1 plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus Study Day 1).

E/C/F/TAF Last Dose Date is the latest of E/C/F/TAF study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued study drug or who completed study drug according to the Study Drug Completion eCRF.

If the date of E/C/F/TAF last dose is missing (eg, only year of last dose is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued or completed study drug, the latest of the E/C/F/TAF study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, excluding the date of the 30-day follow-up visit and any dates on or after the first dose of B/F/TAF if applicable, will be used to impute the last dose date. For other partial missing last dose dates, please see programming specifications (Appendix 7) for imputation rule details.

B/F/TAF Last Dose Date is the latest of B/F/TAF study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued study drug or who completed study drug according to the Study Drug Completion eCRF.

If the date of B/F/TAF last dose is missing (eg, only year of last dose is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued or completed study drug, the latest of the B/F/TAF study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, excluding the date of the 30-day follow-up visit and any dates before the first dose of B/F/TAF, will be used to impute the last dose date. For other partial missing last dose dates, please see programming specifications (Appendix 7) for imputation rule details.

Last Study Date is the latest of E/C/F/TAF or B/F/TAF study drug start date and end date, clinic visit dates, and laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued the study or who completed the study according to Study Completion eCRF.

Baseline value for the E/C/F/TAF phase is defined as the last value obtained on or prior to Study Day 1 for all assessments. Baseline value for the B/F/TAF OL extension phase is defined as the last value obtained on or prior to B/F/TAF Study Day 1 for all assessments.

3.8.2. Analysis Windows

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

3.8.2.1. Analysis Windows for E/C/F/TAF Phase

The analysis windows for HIV-1 RNA, CD4 cell count, CD4%, hematology (excluding INR), chemistry, $eGFR_{CG}$, vital signs, weight, visual analogue scale (VAS), and healthcare utilization assessment are presented in Table 3-1.

Table 3-1. Analysis Windows for HIV-1 RNA, CD4 Cell Count, CD4%, Hematology[a], Chemistry[b], eGFR$_{CG}$, Vital Signs, Weight, Visual Analogue Scale (VAS), and Healthcare Utilization Assessment (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882

a Hematology panel excluding INR and prothrombin time.
b Chemistry profile includes alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase.
Note: The above analysis windows will also be used for bone biomarker of parathyroid hormone (PTH).

The analysis windows for fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides, and total cholesterol to HDL ratio) are presented in Table 3-2.

Table 3-2. Analysis Windows for Fasting Glucose and Lipid Panel (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924

The analysis windows for prothrombin time and INR are presented in Table 3-3.

Table 3-3. Analysis Windows for prothrombin time and INR (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	588
Week 120	840	589	1092

The analysis windows for SF-36 and HIV-TSQc are presented in Table 3-4.

Table 3-4. Analysis Windows for SF-36 and HIV-TSQc (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline[a]			1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924

a HIV TSQc does not have a baseline assessment so analysis window at baseline does not apply.

The analysis windows for HIV-TSQs are presented in Table 3-5.

Table 3-5. Analysis Windows for HIV-TSQs (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	98
Week 24	168	99	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924

The analysis windows for safety ECG are presented in Table 3-6.

Table 3-6. Analysis Windows for Safety ECG (E/C/F/TAF Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week 96	672	505	840

3.8.2.2. Analysis Windows for B/F/TAF OL Extension Phase

The analysis windows for HIV-1 RNA, CD4 cell count, CD4%, hematology, chemistry, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-7.

Table 3-7. Analysis Windows for HIV-1 RNA, CD4 Cell Count, CD4%, Hematology[a], Chemistry[b], $eGFR_{CG}$, Vital Signs, and Weight (B/F/TAF OL Extension Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462

a Hematology panel including PT/INR.
b Chemistry profile includes alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase.
Note: The above analysis windows will also be used for bone biomarker of parathyroid hormone (PTH).

The analysis windows for fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides, and total cholesterol to HDL ratio) are presented in Table 3-8.

Table 3-8. Analysis Windows for Fasting Glucose and Lipid Panel (B/F/TAF OL Extension Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	420

The analysis windows for SF-36 and HIV-TSQ are presented in Table 3-9.

Table 3-9. Analysis Windows for SF-36 and HIV-TSQ (B/F/TAF OL Extension Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	98
Week 24	168	99	252
Week 48	336	253	420

The analysis windows for safety ECG are presented in Table 3-10.

Table 3-10. Analysis Windows for Safety ECG (B/F/TAF OL Extension Phase)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504

3.8.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window. When a single value is needed, the following rule(s) will be used.

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

- For baseline, the latest available record on or prior to the first dose of E/C/F/TAF or B/F/TAF study drug, as appropriate, will be selected. If there are multiple records with the same time or no time recorded on the same day, average will be used for the baseline value, except for HIV-1 RNA (see below).

- For postbaseline visits:

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

  For other numeric observations (except HIV-1 RNA), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the later day will be selected.

  For any numeric observations except HIV-1 RNA, if there are multiple records on the selected day, the average will be taken.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

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

- For baseline, the last available record on or prior to the first dose of E/C/F/TAF or B/F/TAF study drug, as appropriate, will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline visits, the most conservative value within the window will be selected for categorical observations other than patient reported outcomes (eg, abnormal will be selected over normal for safety ECG findings).

- For patient-reported outcomes collected at postbaseline visits, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the later will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects enrolled for each country and investigator will be summarized using the E/C/F/TAF Safety Analysis Set and the B/F/TAF Safety Analysis Set. The denominator for these summaries will be the number of subjects in the respective Safety Analysis Set.

A listing of subject enrollment including date of informed consent signed and met all eligibility criteria will be provided (see Appendix Listing 1).

4.1.2. Subject Disposition

A summary of subject disposition will be provided (see Appendix Table 1). This summary will include the number of subjects screened, screen failure subjects who were not enrolled, subjects who met all eligibility criteria and were not enrolled, subjects enrolled, subjects enrolled but not treated, subjects in the E/C/F/TAF Safety Analysis Set, subjects in the B/F/TAF Safety Analysis Set, subjects in the E/C/F/TAF FAS, and subjects in the B/F/TAF FAS.

In addition, the number and percentage of subjects in the following categories will be summarized:

- Completed E/C/F/TAF study treatment
- Prematurely discontinued E/C/F/TAF study treatment (with summary of reasons for discontinuing study drug)
- Enrolled in the B/F/TAF OL extension phase of the study
- Completed B/F/TAF OL study treatment
- Prematurely discontinued B/F/TAF OL study treatment (with summary of reasons for discontinuing study drug)
- Completed the study
- Prematurely discontinued from the study (with summary of reasons for discontinuing study)

The denominator for the percentages of subjects in each category, except for the categories of "completed B/F/TAF OL study treatment" and "prematurely discontinued B/F/TAF OL study treatment", will be the number of subjects in the E/C/F/TAF Safety Analysis Set. The denominator for the percentage of subjects in the categories of "completed B/F/TAF OL study treatment" and "prematurely discontinued B/F/TAF OL study treatment" will be the number of subjects in the B/F/TAF Safety Analysis Set.

No inferential statistics will be generated. Data listings of reasons for premature study drug discontinuation and premature study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to E/C/F/TAF Study Drug

Duration of exposure to E/C/F/TAF study drug will be defined as (the last E/C/F/TAF dose date Study Day 1 + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure to E/C/F/TAF study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, ie, ≥ 2 weeks (14 days), ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756 days), etc.

Summaries will be provided for subjects in the E/C/F/TAF Safety Analysis Set. No inferential statistics will be provided.

Time to premature discontinuation of E/C/F/TAF study drug will be analyzed using the Kaplan-Meier (KM) method based on the E/C/F/TAF Safety Analysis Set. Subjects who completed E/C/F/TAF study treatment will be censored on the last E/C/F/TAF dose date. A plot of KM estimates for time to premature discontinuation of E/C/F/TAF study drug will be generated.

4.2.2. Duration of Exposure to B/F/TAF Study Drug

Duration of exposure to B/F/TAF study drug will be defined as (the last B/F/TAF dose date B/F/TAF Study Day 1 + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure to B/F/TAF study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, ie, ≥ 2 weeks (14 days), ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), and ≥ 48 weeks (336 days).

Summaries will be provided for subjects in the B/F/TAF Safety Analysis Set. No inferential statistics will be provided.

4.2.3. Adherence with Study Drug

Study drug adherence will be computed based on pill counts. The numbers of pills of study drug dispensed and returned are captured on the Study Drug Accountability eCRF.

Adherence (%) to E/C/F/TAF study drug will be calculated as follows:

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

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

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

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

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

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

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

Adherence will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the E/C/F/TAF study drug for subjects who prematurely discontinued study drug or completed E/C/F/TAF study drug.

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (ie, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for subjects who return at least 1 bottle and have calculable adherence during the study in the E/C/F/TAF Safety Analysis Set. No inferential statistics will be provided.

Adherence will be calculated in a similar manner for the B/F/TAF Safety Analysis Set.

4.3. Protocol Deviations

A listing will be provided for subjects in the All Enrolled Subjects analysis set who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex at birth, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The summaries of demographic data and baseline characteristics will be provided for the E/C/F/TAF Safety Analysis Set and the B/F/TAF Safety Analysis Set. Baseline for each phase is defined in Section 3.8.1.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics collected at enrollment will be summarized:

- Mode of infection (HIV risk factors)
- HIV disease status at study entry
- HCV antibody status at study entry
- Medical history at study entry: Type I or II diabetes (Yes/No), cardiovascular disease (Yes/No), hypertension (Yes/No), and hyperlipidemia (Yes/No) (see Appendix 7 for details)
- Smoking status at study entry: (a) Never Smoked, (b) Former Smoker, and (c) Current Smoker (see Appendix 7 for details)
- Duration of hemodialysis at study entry (years)
- Pre-switch ARV categories: (a) Containing TDF, (b) Containing ABC, and (c) Containing Neither
- Pre-switch ARV categories: (a) Containing 3TC, (b) Containing ABC, (c) Containing TDF, (d) Containing FTC
- Pre-switch ARV 3rd Agent Category: (a) INSTI, (b) PI, (c) NNRTI, (d) CCR5 Antagonist

The following baseline disease characteristics collected prior to E/C/F/TAF administration and prior to B/F/TAF administration will be summarized for the E/C/F/TAF Safety Analysis Set and the B/F/TAF Safety Analysis Set, respectively:

- HIV-1 RNA categories (copies/mL): (a) < 50 and (b) ≥ 50
- CD4 cell count (/µL)
- CD4 cell count categories (/µL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500

- CD4%
- $eGFR_{CG}$ (mL/min)

No inferential statistics will be provided.

5.3. Medical History

Subjects' answers to the following questions prespecified on the Medical History CRF will be listed:

- Does the Subject have diabetes? (Type I or II)
- Have any first-degree relatives experienced MI or stroke before the age of 50?

In addition, subjects' kidney transplant registration status collected by the Transplant History CRF will be listed.

General medical history data will be collected at screening and listed only. General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

6. ANALYSES OF PRIMARY ENDPOINT

6.1. Definition of the Primary Endpoint

The primary endpoint of this study is the incidence of treatment-emergent Grade 3 or higher AEs in subjects receiving E/C/F/TAF up to Week 48. The analysis of the primary endpoint was conducted for the Week 48 clinical study report and will not be repeated for this final analysis.

7. EFFICACY ANALYSES

The proportions of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm were summarized as part of the Week 48 clinical study report and will not be repeated for the final analysis.

7.1. Efficacy Endpoints as Secondary Study Endpoints

Secondary efficacy endpoints for the final analysis include the following:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as defined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL by visit
- The change from baseline in CD4 cell count and CD4% by visit

7.2. Analysis of Efficacy Endpoints

7.2.1. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 96 as Determined by US FDA-defined Snapshot Algorithm

US FDA-Defined Snapshot Algorithm

The analysis window at Week 96 is defined as from Study Day 631 to Study Day 714, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date of E/C/F/TAF study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome for Week 96 will be defined using the following categories:

- **HIV-1 RNA < 50 copies/mL**: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the analysis window
- HIV-1 RNA ≥ 50 copies/mL: this includes subjects
  1) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the analysis window , or
  2) Who do not have on-treatment HIV-1 RNA data in the analysis window and
     a) Who discontinue study drug prior to or in the analysis window due to lack of efficacy, or
     b) Who discontinue study drug prior to or in the analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
     c) Who discontinue study drug prior to or in the 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 Window**: this includes subjects who do not have on-treatment HIV-1 RNA data in the analysis window because of the following:

  3) Discontinuation of study drug prior to or in the analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

  4) Discontinuation of study drug prior to or in the analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA is < 50 copies/mL, or

  5) Missing data during the window but on study drug

The flowchart of the snapshot algorithm is provided in Appendix 3.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 96 will be summarized using the E/C/F/TAF FAS. The 95% confidence intervals (CIs) for percentages of subjects with HIV-1 RNA < 50 copies/mL and HIV-1 RNA ≥ 50 copies/mL will be constructed using the Exact method (see Appendix Table 1Appendix Table 2).

The same analysis will be repeated for proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 96 as defined by US FDA-defined snapshot algorithm.

The Week 96 virologic outcomes for the US FDA-defined snapshot algorithm will be listed (see Appendix Listing 2).

7.2.2. Analysis of Other Efficacy Endpoints

7.2.2.1. By-Visit Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL by Missing Failure and Missing Excluded Approaches

The proportion of subjects with HIV-1 RNA < 50 copies/mL will be summarized using the following 2 methods for imputing missing HIV-1 RNA values:

- Missing Failure (M F)

In this approach, all missing data will be treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages is the number of subjects in the E/C/F/TAF FAS.

- Missing Excluded (M E)

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

For both M F and M E analyses, the number and percentage of subjects with HIV-1 RNA in the following categories will be summarized (see Appendix Table 3):

- < 50 copies/mL

  < 20 copies/mL

  - < 20 Not Detectable
  - < 20 Detectable

- 20 to < 50 copies/mL
- ≥ 50 copies/mL

The 95% CIs of the proportion of subjects with HIV-1 RNA < 50 copies/mL will be provided using the Exact method.

Separate summaries will be provided for the E/C/F/TAF FAS and the B/F/TAF FAS.

7.2.2.2. Analysis of CD4 Cell Count and CD4 %

Values and changes from baseline in CD4 cell count and CD4% will be summarized at each postbaseline visit using descriptive statistics based on observed on-treatment values. On-treatment values include data collected after the first dose date up to the applicable last dose date + 1 day for subjects who permanently discontinued the applicable study drug.

In addition, values and changes from baseline in CD4 cell counts with missing values imputed using the last observation carried forward (LOCF) method will be summarized at each postbaseline visit. The algorithm for LOCF is as follows:

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value (ie, up to 1 day after the last dose date of applicable study drug) observed before the analysis visit window that has the missing value.
- Baseline values will not be used for imputation; subjects who had no postbaseline CD4 assessment will be excluded from the postbaseline summaries.

The mean and 95% CI and median (Q1, Q3) of values and change from baseline in CD4 cell count over time will be plotted using observed data.

Separate summaries will be provided for the E/C/F/TAF FAS and the B/F/TAF FAS.

7.3. Changes From Protocol-Specified Efficacy Analyses

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

8. SAFETY ANALYSES

Safety data will be summarized for the subjects in the E/C/F/TAF Safety Analysis Set and the B/F/TAF Safety Analysis Set. All safety data will be included in data listings.

The primary endpoint of the incidence of treatment-emergent Grade 3 or higher AEs up to Week 48 was conducted for the Week 48 clinical study report and will not be repeated for this final analysis.

The secondary endpoint of the incidence of treatment-emergent Grade 3 or higher AEs up to Week 96 is defined in a similar manner to the primary endpoint included in the Week 48 clinical study report (See Section 8.1).

E/C/F/TAF Phase

For subjects who do not participate in the B/F/TAF OL extension phase, all safety data collected from the first dose of E/C/F/TAF up to 30 days after permanent discontinuation of E/C/F/TAF study drug will be summarized, unless specified otherwise. For subjects who participate in the B/F/TAF OL extension phase, all safety data collected up to the date of the first B/F/TAF study drug dose will be summarized, unless specified otherwise.

B/F/TAF OL Extension Phase

All safety data collected from the first dose of B/F/TAF up to 30 days after permanent discontinuation of B/F/TAF study drug will be summarized, unless specified otherwise.

8.1. Adverse Events Up to Week 96

Adverse events up to Week 96, or adverse events on or prior to Week 96, refers to those adverse events with onset date (if applicable) on or prior to the date of the Week 96 visit, as recorded on the Visit Date CRF, for subjects who had the Week 96 visit performed according to the Visit Date CRF.

If the onset date of an AE is partially missing (with only year and month or year alone), the event is considered on or prior to Week 96 if the month and year (or year alone) of the AE onset date is the same as or before the month and year (or year) of the Week 96 visit date recorded on the Visit Date CRF.

If the onset date of an AE in completely missing, the event is considered on or prior to the Week 96 if any of the following three criteria are met:

- The AE stop date is on or prior to the Week 96 visit date; or
- The AE stop date is partially missing, with the month and year (or year alone) on or prior to the Week 96 visit date; or
- The AE stop date is completely missing, including the case when AE is still ongoing.

For subjects who prematurely discontinued the study prior to the Week 96 visit, all adverse events will be considered AEs on or prior to Week 96.

8.2. Analysis of Adverse Events Up to Week 96

The number and percentage of subjects who experienced at least 1 Grade 3 or 4 treatment-emergent AE will be provided by system organ class (SOC) and preferred term (PT) using the E/C/F/TAF Safety Analysis set. For those AEs that occurred more than once in an individual subject during the specified time frame, the most severe grade will be used.

Multiple events will be counted only once per subject in the summaries. Adverse events will be summarized and listed first in alphabetical order of SOC, and then by PT in descending order of total frequency within each SOC. Grade 3 or 4 treatment-emergent AEs will also be summarized by PT only, in descending order of total frequency.

Grade 3 or 4 treatment-emergent study-drug related AEs by Week 96 will be summarized by SOC and PT.

The general safety summaries described in Section 8.3 will present all TEAEs (or subset of TEAEs).

8.3. Adverse Events and Deaths

8.3.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). SOC, high-level group term (HLGT), high level term (HLT), PT, and lowest-level term (LLT) will be provided in the AE dataset.

8.3.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life threatening) according to toxicity criteria specified in the study protocol. The severity grade of events for which the investigator did not record severity will be left as “missing” for data listings.

8.3.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment”. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

8.3.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs meet the definition of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance & Epidemiology Department before data finalization.

8.3.5. Treatment-Emergent Adverse Events

8.3.5.1. Definition of Treatment-Emergent Adverse Events

E/C/F/TAF phase treatment-emergent AEs are defined as 1 or both of the following:

- Any AEs with an onset date on or after the E/C/F/TAF study drug start date and no later than 30 days after permanent discontinuation of the E/C/F/TAF study drug for subjects who do not participate in the B/F/TAF OL extension phase or the day prior to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension phase, or

- Any AEs leading to premature discontinuation of E/C/F/TAF study drug.

B/F/TAF OL extension phase treatment-emergent AEs are defined as 1 or both of the following:

- Any AEs with an onset date on or after the B/F/TAF study drug start date and no later than 30 days after permanent discontinuation of the B/F/TAF study drug, or

- Any AEs leading to premature discontinuation of B/F/TAF study drug.

8.3.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dose date of E/C/F/TAF study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent.

The event is considered treatment emergent for the E/C/F/TAF phase if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is **the same as or after** the month and year (or year) of the first dose date of E/C/F/TAF study drug, and

- The month and year (or year) of the AE onset is **the same as or before** the month and year (or year) of the date corresponding to the minimum of (1) the last dose of E/C/F/TAF study drug plus 30 days AND (2) the first dose of B/F/TAF study drug minus 1 day

The event is considered treatment emergent for the B/F/TAF OL extension phase if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is **after** the month and year (or year) of the first dose date of B/F/TAF study drug, and
- The month and year (or year) of the AE onset is **the same as or before** the month and year (or year) of the date corresponding to 30 days after the date of last dose of B/F/TAF study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date on or after the first dose date of E/C/F/TAF study drug, will be considered to be treatment emergent for the E/C/F/TAF phase. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dose date of E/C/F/TAF study drug will be considered treatment emergent.

8.3.6. Summaries of Adverse Events and Deaths

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, and PT separately for the E/C/F/TAF Safety Analysis Set and B/F/TAF Safety Analysis Set. For other AEs described below, summaries will be provided by SOC and PT separately for the E/C/F/TAF Safety Analysis Set and B/F/TAF Safety Analysis Set:

- Any Grade 2, 3, or 4 treatment-emergent AE
- Any Grade 3 or 4 treatment-emergent AE
- All treatment-emergent study-drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study-drug-related AE
- Any Grade 3 or 4 treatment-emergent study-drug-related AE
- All treatment-emergent SAEs
- All treatment-emergent study-drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

A brief, high-level summary of AEs described above will be provided by the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths observed in the study will also be included in this summary.

For the E/C/F/TAF Safety Analysis Set summary, treatment-emergent death refers to a death that occurred between the first E/C/F/TAF dose date and the last E/C/F/TAF dose date plus 30 days (inclusive) for subjects who do not participate in the B/F/TAF OL extension phase or the day prior to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension phase.

For the B/F/TAF Safety Analysis Set summary, treatment-emergent death refers to a death that occurred between the first B/F/TAF dose date and the last B/F/TAF dose date plus 30 days (inclusive).

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetical order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all treatment-emergent AEs will be summarized by PT only, in descending order of total frequency.

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

- All AEs (with a variable indicating whether the event is treatment-emergent)
- Grade 3 and 4 AEs
- Study-drug-related AEs
- SAEs
- Study-drug-related SAEs
- Deaths reported
- AEs leading to premature discontinuation of study drug.

8.3.7. Additional Analysis of Adverse Events

8.3.7.1. Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnosis (see Protocol Appendix 8). The Gilead medical monitor will review the possible stage 3 opportunistic illnesses and approve the events that meet the definition. Events that meet the stage 3 opportunistic illnesses definition diagnosis will be listed for all enrolled subjects.

8.3.7.2. Common Adverse Events Included in the FTC Prescribing Information

The common treatment-emergent AEs in the FTC Prescribing Information will be summarized by PT, in descending order of total frequency. The associated PTs are the following:

- Headache
- Diarrhea
- Nausea
- Fatigue
- Dizziness
- Depression
- Insomnia
- Abnormal dreams
- Rash
- Abdominal pain
- Asthenia
- Cough
- Rhinitis.

A by-subject listing will be provided for AEs with PT terms above for all enrolled subjects.

8.3.7.3. Cardiovascular or Cerebrovascular Events

Preferred terms for cardiovascular or cerebrovascular events are from relevant Standardised MedDRA Query (SMQ). The selected PT listing was provided by Gilead PVE and reviewed by Gilead medical monitors (see details in Appendix 4).

A data listing of cardiovascular or cerebrovascular events will be provided for the B/F/TAF Safety Analysis Set.

8.3.7.4. Hepatic Events

Preferred terms for hepatic events are from 15 relevant SMQs, which are identified as non-infectious and non-congenital hepatobiliary disorders. The selected PT listing was provided by Gilead PVE and reviewed by Gilead medical monitors (see details in Appendix 5).

A data listing of hepatic events will be provided for the B/F/TAF Safety Analysis Set.

8.4. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the E/C/F/TAF Safety Analysis Set and B/F/TAF Safety Analysis Set. The analysis will be based on values reported in conventional units. When values are below the lower limit of quantitation they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology and serum chemistry separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

8.4.1. Summaries of Numeric Laboratory Results

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

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

In addition, percentage change from baseline at each postbaseline analysis window will also be provided for biomarker PTH.

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

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

Calcium Corrected for Albumin

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

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

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

Estimated GFR

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

- $eGFR_{CG}$ (mL/min) [(140 age(yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms, and SCr is serum creatinine.

8.4.2. Graded Laboratory Values

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

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

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

For international normalized ratio (INR) of prothrombin time, protocol-specified toxicity grade scale depends on the upper limit of normal range (ULN). While the ULN of INR depends on whether a subject is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 - 1.2; Taking oral anticoagulant: 2.0 3.0), the information is not collected in Covance lab. As a result, INR will be graded by assuming the subject is not taking oral anticoagulant, which is a more conservative approach and may lead to over-reporting abnormalities for INR. Since INR and prothrombin time are reflex tests; only an absolute value and not the toxicity grade is needed for patient management purposes; most importantly, the toxicity grades for INR may be over-reported. INR and prothrombin time will not be included in the laboratory abnormalities summary tables but will be included in a listing.

8.4.2.1. Treatment-Emergent Laboratory Abnormalities

E/C/F/TAF treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point up to 30 days after the permanent discontinuation of E/C/F/TAF study drug for subjects who do not participate in the B/F/TAF OL extension phase or up to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension phase.

B/F/TAF treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point up to 30 days after the permanent discontinuation of B/F/TAF study drug.

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

Fasting glucose and nonfasting glucose (including glucose result without a known fasting status) are graded based on different grading scales as specified in the protocol. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Maximum postbaseline grade, instead of treatment-emergent grade, for nonfasting glucose will be summarized, as nonfasting glucose was not assessed at baseline visit for most of the subjects; therefore, whether an abnormality is treatment-emergent or not cannot be determined for these subjects.

8.4.2.2. Summaries of Laboratory Abnormalities

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

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 or 4 laboratory abnormalities

For all summaries of E/C/F/TAF laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline values up to 30 days after the last E/C/F/TAF dose date for subjects who do not participate in the B/F/TAF OL extension phase or up to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension phase.

For all summaries of B/F/TAF laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline values up to 30 days after the last B/F/TAF dose date.

By-subject listings of treatment-emergent graded abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

8.4.3. Metabolic Laboratory Evaluations

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

Fasting lipid data will also be analyzed by using the following National Cholesterol Education Program (NCEP) ATP III categories {National Cholesterol Education Program (NCEP) 2001}:

- For total cholesterol (mg/dL): < 200, 200-239, ≥ 240
- For LDL (mg/dL): <100, 100-129, 130-159, 160-189, and ≥ 190
- For HDL (mg/dL): < 40, ≥ 40 to < 60, and ≥ 60
- For triglycerides (mg/dL): < 150, 150-199, 200-499, and ≥ 500

The number and proportion of subjects for the above categories of each lipid parameter will be summarized by its baseline category at Weeks 24, 48, 72, and 96 for the E/C/F/TAF Safety Analysis Set and at Weeks 24 and 48 for the B/F/TAF Safety Analysis Set.

In addition, the number and proportion of subjects in the E/C/F/TAF Safety Analysis Set who took lipid modifying medication at study entry and initiated medication during the E/C/F/TAF phase and the number and proportion of subjects in the B/F/TAF Safety Analysis Set who took lipid modifying medication at the start of the B/F/TAF OL extension phase and initiated medication during the B/F/TAF OL extension phase will be provided.

A lipid modifying medication is defined as a medication with drug class (Anatomical Therapeutic Chemical drug class Level 2) "LIPID MODIFYING AGENTS" and CMDECOD containing the wording of "STATIN".

A sensitivity analysis of fasting lipid tests (including total cholesterol, LDL, HDL, triglycerides, and total cholesterol to HDL ratio) will be performed using the E/C/F/TAF Safety Analysis Set by excluding subjects who took lipid modifying medication at study entry or initiated lipid modifying medication during the study prior to Week 96: baseline, postbaseline, and changes from baseline at Week 96 will be summarized. Only subjects with both baseline and Week 96 postbaseline values will be included in the analysis.

A sensitivity analysis of fasting lipid tests (including total cholesterol, LDL, HDL, triglycerides, and total cholesterol to HDL ratio) will be performed using the B/F/TAF Safety Analysis Set by excluding subjects who took lipid modifying medication at the start of the B/F/TAF OL extension phase or initiated lipid modifying medication during the B/F/TAF OL extension phase: baseline, postbaseline, and changes from baseline at Weeks 24 and 48 will be summarized. Only subjects with both baseline and Week 48 postbaseline values will be included in the analysis.

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted.

8.4.4. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements (see Appendix Table 4):

Individual Test:

- Aspartate aminotransferase (AST): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline Phosphatase (ALP): > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The E/C/F/TAF summary will use data from all postbaseline visits up to 30 days after the last dose of E/C/F/TAF study drug for subjects who do not participate in the B/F/TAF OL extension phase or up to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension phase.

The B/F/TAF summary will use data from all postbaseline visits up to 30 days after the last dose of B/F/TAF study drug.

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the E/C/F/TAF Safety Analysis Set or B/F/TAF Safety Analysis Set with nonmissing postbaseline values of the tests in evaluation at the same postbaseline visit date.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by visit using descriptive statistics.

Subjects with AST or ALT > 3 × ULN will also be listed.

8.5. Vital Signs and Body Weight

Descriptive statistics will be provided for vital signs and body weight as follows:

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

A baseline value for the E/C/F/TAF phase will be defined as the last nonmissing value obtained on or prior to the date of first dose of E/C/F/TAF study drug. A baseline value for the B/F/TAF OL phase will be defined as the last nonmissing value obtained on or prior to the date of first dose of B/F/TAF study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

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

A by-subject listing of vital signs, body weight, height, and BMI will be provided by subject ID number and visit in chronological order.

8.6. Prior and Concomitant Medications

8.6.1. Nonstudy-Drug Antiretroviral (ARV) Medications

Any nonstudy-drug ARV medications used prior to, during, or after the study (if collected) will be coded using the GSI-modified World Health Organization (WHO) Drug Dictionary for ARV medications. The WHO preferred name and drug code will be attached to the clinical database. All nonstudy-drug ARV medications will be listed. No inferential statistics will be provided.

8.6.1.1. Nonstudy-Drug ARV Medication Received at Baseline

Nonstudy-drug ARV medication with an end date 1 or 2 days before the first dose date of E/C/F/TAF study drug will be considered as nonstudy-drug ARV medication received immediately prior to the first E/C/F/TAF dose date of study drug (or prior ARV used at baseline [pre-switch]).

Nonstudy-drug ARV medication received immediately prior to the first dose date of E/C/F/TAF study drug will be summarized by preferred name for subjects in the E/C/F/TAF Safety Analysis Set. Multiple drug use (by preferred name) will be counted only once per subject. Preferred names will be presented by descending order of the total frequency. No inferential statistics will be provided.

8.6.1.2. Nonstudy-Drug ARV Medication Received Prior to the First Dose Date of Study Drug

Nonstudy-drug ARV medication received prior to the first dose date of E/C/F/TAF study drug will also be summarized as a separate table. Results will be summarized in the same way as described for prior ARV used at baseline in Section 8.6.1.1.

8.6.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant non-ARV medications from Study Day 1 up to the date of last dose of E/C/F/TAF study drug will be summarized (number and percentage of subjects) by preferred name for the E/C/F/TAF Safety Analysis Set. Use of concomitant non-ARV medications from B/F/TAF Study Day 1 up to the date of last dose of B/F/TAF study drug will be summarized (number and percentage of subjects) by preferred name for the B/F/TAF Safety Analysis Set. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be presented by decreasing total frequency.

If the start or stop date of a non-ARV medication is incomplete, the month and year (or year alone if month is not recorded) of start or stop date determine whether the non-ARV is concomitant or not. The medication is concomitant if the month and year of start or stop (or year of the start or stop) of the medication does not meet either of the following criteria:

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

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

Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

8.7. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each scheduled postbaseline visit (Weeks 48 and 96 for the E/C/F/TAF Safety Analysis Set and Week 48 for the B/F/TAF Safety Analysis Set) compared with baseline values will be presented using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; and missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No inferential statistics will be provided.

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

8.8. Healthcare Utilization Assessment

The number of hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits for a healthcare issue since the last study visit were summarized for the Week 96 analysis and will not be repeated for the final analysis.

A listing of healthcare utilization assessment data will be provided by subject.

8.9. Other Safety Analysis

A data listing will be provided for subjects experiencing pregnancy during the study. Physical examination data were not collected in the eCRF; therefore, there is no analysis for these data.

8.10. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analyses is planned.

9. PHARMACOKINETIC ANALYSES

CCI [redacted]

During the B/F/TAF OL extension phase, at Weeks 4 OL, 24 OL, and 48 OL, on the day of hemodialysis, a sparse timed blood sample was to be collected from all subjects within 10 minutes prior to hemodialysis initiation. Predose (within 30 minutes prior to study drug administration) blood draws for plasma samples were also collected at these visits.

Plasma concentrations of bictegravir from the pre-hemodialysis and pre-dose (post-hemodialysis) PK draws at Weeks 4 OL, 24 OL, and 48 OL will be listed for all subjects for the B/F/TAF Plasma PK Analysis Set.

Concentration samples will be summarized using descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI) for the B/F/TAF Plasma PK Analysis Set. For concentration values below the limit of quantitation (BLQ), the number of subjects with values BLQ will be presented.

Plasma PK sampling details and study drug administration records for plasma PK samples for the B/F/TAF OL extension phase will be listed.

10. PATIENT REPORTED OUTCOMES

Patient reported outcomes (PRO) include the following assessments:

- Medication Adherence Questionnaire (assessed at all protocol planned visits through Week 96 for E/C/F/TAF phase)
- HIV Treatment Satisfaction Questionnaire Status (HIV-TSQs) (assessed at baseline, Weeks 4, 24, 48, 72, 96, and End of E/C/F/TAF Visit for E/C/F/TAF phase and at Weeks 4 OL, 24 OL, and 48 OL for B/F/TAF OL extension phase)
- HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc) (assessed at Weeks 24, 48, 72, 96, and End of E/C/F/TAF Visit for E/C/F/TAF phase)
- Medical Outcome Study Short Form (SF-36) (assessed at Baseline, Weeks 24, 48, 72, 96, and End of E/C/F/TAF Visit for E/C/F/TAF phase and at Weeks 4 OL, 24 OL, and 48 OL for B/F/TAF OL extension phase)

The Medication Adherence Questionnaire will be listed only.

The HIV-TSQs, HIV-TSQc, and SF-36 results will be summarized using the E/C/F/TAF Safety Analysis Set. Data collected up to 30 days after the last dose date of E/C/F/TAF study drug for subjects who do not participate in the B/F/TAF OL extension or up to the date of the first B/F/TAF study drug dose for subjects who participate in the B/F/TAF OL extension will be included in summaries.

The HIV-TSQs and SF-36 results will also be summarized using the B/F/TAF Safety Analysis Set. Data collected up to 30 days after the last dose date of B/F/TAF study drug will be included in summaries.

Unless otherwise stated, multiple responses and out of range responses will be set to missing and missing responses will not be imputed. The PRO data will be listed.

10.1. Medication Adherence Questionnaire

Adherence was assessed by the medication adherence questionnaire that includes a VAS and 2 additional questions.

For the VAS, the subject is asked to describe their adherence to their ARV regimen by using a linear scale (0% 100%) to indicate what percent of medication was taken in the last 30 days (0% taken none of prescribed anti-HIV medication, and 100% taken all doses of prescribed anti-HIV medication). The 2 additional questions ask how many days the subject has missed medication in the last 30 days and how many days the subject has missed medication in the last 4 days.

A listing will be provided for subject response to the VAS questionnaire.

10.2. HIV Treatment Satisfaction Questionnaire

Both HIV-TSQs and HIV-TSQc forms have 10 questions about the current treatment regimen.

For the Status form, the responses to those questions range from (6) very satisfied, to (0) very dissatisfied; for the Change form, the responses to those questions range from (3) much more satisfied now, to (-3) much less satisfied now, with the exception of the following questions:

a) How well controlled do you feel your HIV has been recently? For Status form: (6) very well controlled, to (0) very poorly controlled; for Change form: (3) much better controlled now, to (-3) much worse controlled now;

b) How convenient have you been finding your treatment to be recently? For Status form: (6) very convenient, to (0) very inconvenient; for Change form: (3) much more convenient now, to (-3) much less convenient now;

c) How flexible have you been finding your treatment to be recently? For Status form: (6) very flexible, to (0) very inflexible; for Change form: (3) much more flexible now, to (-3) much less flexible now;

d) On Status form only: Would you recommend your present treatment to someone else with HIV? (6) Yes, I would definitely recommend the treatment, to (0) No, I would definitely not recommend the treatment.

e) On Change form only: How likely would you be to recommend your present treatment to someone else with HIV? (3) much more likely to recommend the treatment now, to (-3) much less likely to recommend the treatment now.

A treatment satisfaction scale total will be calculated as the sum of the responses to the 10 question items on the Status form, ranging from 0 to 60, and on the Change form, ranging from 30 to 30. If the number of missing responses is ≥ 2 then the treatment satisfaction scale total will be set to missing; otherwise, the missing item score will be imputed by the average of the non-missing item responses from the same subject at the same visit and the treatment satisfaction scale total will be calculated.

A descriptive summary of the number and percent of subjects with responses to each question and the treatment satisfaction scale total will be provided for HIV-TSQs form and the HIV-TSQc form by visit.

Two listings will be provided for subject responses to HIV-TSQs and HIV-TSQc forms at all visits for each subject, respectively.

10.3. SF-36 (Version 2) Health Survey

The SF-36 Version 2 is a self-reported, generic, comprehensive, and widely used questionnaire that is designed to measure health-related quality of life in the general population, as well as in subject groups with diverse chronic diseases including HIV/AIDS. Responses from the 36 items are used to construct 8 health domains including physical functioning, social functioning, general health, vitality, bodily pain, mental health, role capacity-physical, and role capacity-emotional. Furthermore, 2 summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, aggregate information from the 8 SF-36 domains in a way that captures 80% to 85% of the variance in the 8 domains.

10.3.1. Scoring the SF-36

The 8 domains and 2 component summary scores of the SF-36 will be calculated according to "How to Score Version 2 of the SF-36 Health Survey (Chapters 6 and 7)" {Maruish 2011} published by QualityMetric Inc. Scores for each of the 8 domains, including PCS and MCS, range from 0 to 100 with a higher score indicating a better functioning.

10.3.2. SF-36 Statistical Analysis Method

Scores and change from baseline for each domain, PCS, and MCS will be summarized by visit using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum).

A by-subject listing for the scores for each domain, PCS, and MCS will be provided.

11. REFERENCES

Maruish ME. User's manual for the SF-36v2 Health Survey. 3rd ed. Lincoln, RI: Quality Metric Incorporated.; 2011.

National Cholesterol Education Program (NCEP). Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. National Institute of Health May, 2001.

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

12. SOFTWARE

SAS® (SAS Institute Inc., Version 9.4, Cary, NC) is to be used for all programming of tables, listings, and figures.

nQuery Advisor® (Statistical Solutions Ltd., Version 6.0, Cork, Ireland) was used for the sample size and power calculation.

13. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

14. APPENDICES

Appendix 1. Study Procedures Table (E/C/F/TAF Phase)

Study Procedure	Screen[a]	Day 1[b]	Week 2 to Week 96[c]											Post Week 96	End of E/C/F/TAF Visit	30-Day Follow-up[d]	ESDD[e]
			2	4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Written Informed Consent	X																
Medical History	X																
Complete Physical Examination[f]	X	X					X		X				X				X
Symptom directed Physical Examination[g]			X	X	X	X		X		X	X	X		X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X
Height	X																
12 Lead ECG	X								X				X		X		X
Chemistry Profile[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[j]		X					X[j]		X[j]		X[j]		X[j]	X[w]	X		
Serum Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ T Cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV 1 RNA[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV 1 Genotype/Phenotype[m]			X	X	X	X	X	X	X	X	X	X	X	X	X		X
Estimated eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology profile[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Samples		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CCI																	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV and HCV Serology[p]	X																

Study Procedure	Screen[a]	Day 1[b]	Week 2 to Week 96[c]											Post Week 96	End of E/C/F/TAF Visit	30-Day Follow-up[d]	ESDD[e]
			2	4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF 36[q]		X					X		X		X		X		X		X
HIV TSQ[q]	X	X		X			X		X		X		X		X		X
VAS		X	X	X	X	X	X	X	X	X	X	X	X				X
Health Utilization Assessment[r]		X	X	X	X	X	X	X	X	X	X	X	X				X
Drug Dispensation and Accountability		X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X[x]		X[s]
Pre dose Whole Blood Sample Collection[t]				X		X											
CCI																	
Whole Blood Storage Sample[v]		X															

a Evaluations to be completed within 30 days prior to Day 1.
b Subjects will be dispensed study drug on the Day 1 Visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 Visit.
c All study visits are to be scheduled relative to the Day 1 Visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 6 days of the protocol specified date through Week 48, except Week 48. Weeks 48 Visit window is ± 6 weeks of the protocol specified date. Week 48 Visit should be completed within ± 6 day window, unless otherwise specified by the Sponsor. Following the Week 48 Visit, study visits are to be completed within ± 6 days of the protocol specified date through Week 84. The visit window at Week 96 will be ± 6 weeks of the protocol specific visit date. Unless notified by the Sponsor, Week 96 Visit should be completed within ± 6 days of the protocol specific visit date.
d Required for those subjects who complete Week 96 Visit or those subjects who prematurely 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 Early Study Drug Discontinuation Visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 96, if the subject discontinues study drug prior to completion of Week 96 Visit.
f Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator).
g Symptom directed physical examination as needed
h Weight only
i Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, PT/INR, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH. At Day 1, Weeks 24, 48, 72, and 96 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. PT/INR will be included in the chemistry profile at Screening, Weeks 24 and 48 only. This sample should be drawn prior to hemodialysis. The timing of draw and timing of hemodialysis should be recorded.

j Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, 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. At Weeks 24, 48, 72, and 96 analyses of glucose will be done as part of fasting metabolic assessments and not as part of the chemistry profile.

k Females of childbearing potential only. FSH test is required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

l If the HIV 1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2 4 weeks after the date of the original test (except for screening and baseline results). See Protocol Section 6.7.1.

m HIV 1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic rebound with HIV 1 RNA value ≥ 400 copies/mL. Subjects should be managed according to the Virologic Rebound Schema (see Protocol Section 6.7.1). HIV 1 genotype/phenotype sample collection to occur if subject's HIV 1 RNA lab values meet the criteria described in this section.

n CBC with differential and platelet count

[redacted]

p See Protocol Section 4.2 to confirm subject eligibility prior to enrollment.

q SF 36 is to be completed by subjects at Day 1, Week 24, Week 48, Week 72, and Week 96 Visits. HIV TSQs should be completed by the subjects at Screening, Day 1, Week 4, Week 24, Week 48, Week 72, Week 96 and ESDD Visits. HIV TSQc should be completed by the subjects at Week 24, Week 48, Week 72, Week 96 and ESDD Visits.

r Subjects will be asked about their health utilization at Day 1 Visit and every visit thereafter, including the ESDD and Unscheduled Visits.

s Drug accountability only; study drug will not be dispensed at these visits.

t At Week 4 or Week 12, pre dose whole blood sample will be collected for subjects enrolled in the study. Sample collection should occur within 30 minutes prior to the study drug administration which should be observed on site. PBMC processing will be completed by the central laboratory.

[redacted]

v Whole blood storage sample collected at baseline visit for virology assessments.

w Every 24 Weeks

x Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the Open Label Rollover extension for at least 48 weeks.

Appendix 2. Study Procedures Table (Open Label Rollover Extension)

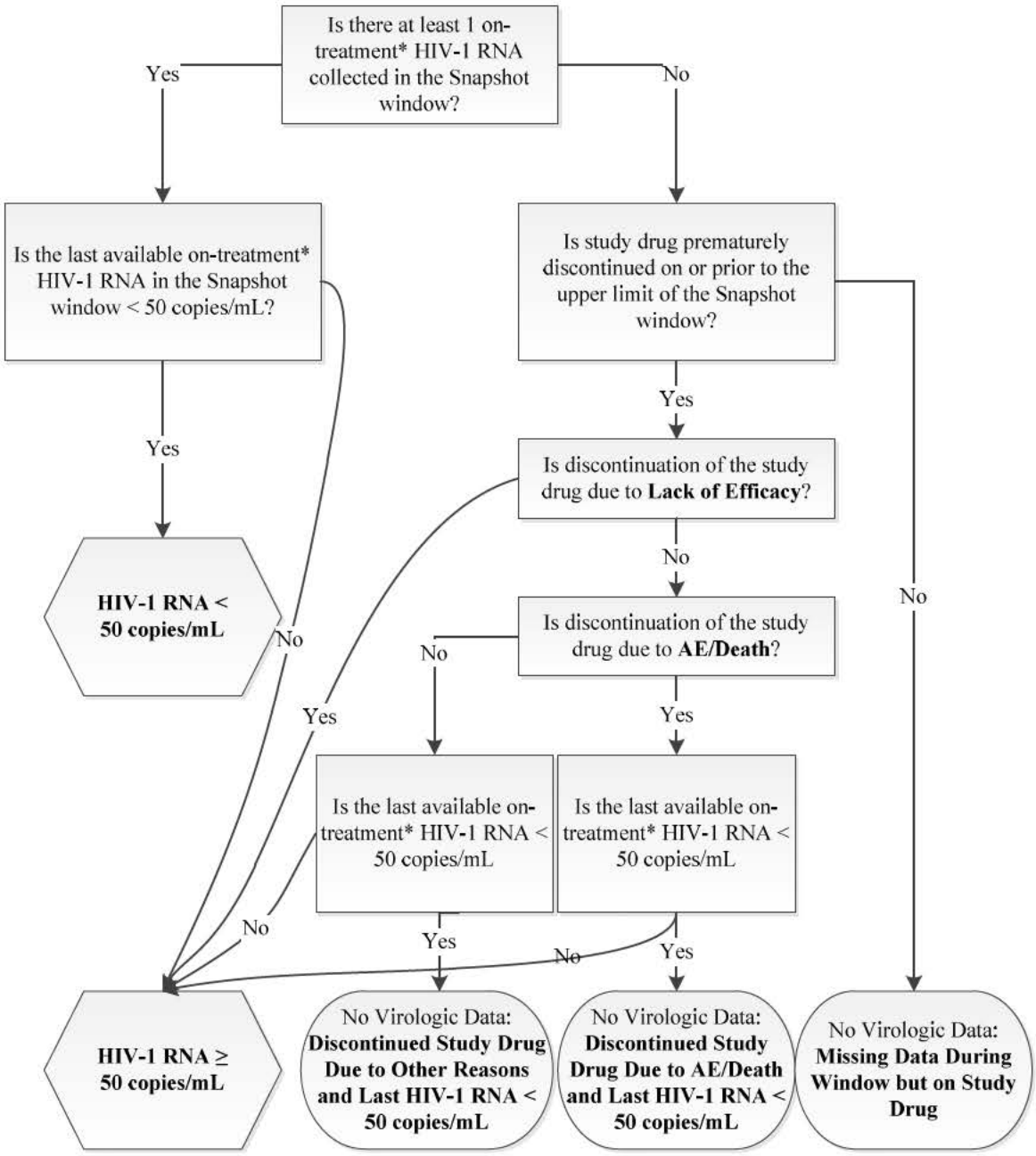
Study Procedure	End of E/C/F/TAF Visit	End of Week[a, c]					30-Day Follow-up[d]	ESDD[e]
		Week 4 OL	Week 12 OL	Week 24 OL	Week 36 OL	Week 48 OL		
Complete Physical Examination[f]						X		X
Symptom directed Physical Examination[g]	X	X	X	X	X		X	
Vital Signs and Weight	X	X	X	X	X	X	X[h]	X
12 Lead ECG	X					X		X
Chemistry Profile[i]	X	X	X	X	X	X	X	X
Metabolic Assessments[j]	X			X		X		
Serum Pregnancy Test[k]	X	X	X	X	X	X	X	X
CD4+ T Cell Count	X	X	X	X	X	X	X	X
Plasma HIV 1 RNA[l]	X	X	X	X	X	X	X	X
HIV 1 Genotype/Phenotype[m]	X	X	X	X	X	X		X
PK Sampling[p]		X		X		X		
Estimated eGFR	X	X	X	X	X	X		X
Hematology profile[n]	X	X	X	X	X	X	X	X
Plasma Storage Samples	X	X	X	X	X	X		X
CCI								
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
SF 36	X	X		X		X		X
HIV TSQ	X	X		X		X		X
Drug Dispensation and Accountability	X	X	X	X	X	X		X[b]

a Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the Open Label Rollover extension for at least 48 weeks.
b Drug accountability only; study drug will not be dispensed at these visits
c All study visits are to be scheduled based upon the Week 96 Visit or End of E/C/F/TAF Visit date (whichever occurs later). The Week 4 OL Visit should be completed within ±2 days of the protocol specified visit date. All other Study visits are to be completed within ± 6 days of the protocol specified visit date, unless otherwise specified by the Sponsor.

d Required for those subjects who complete End of E/C/F/TAF Visit or those subjects who prematurely discontinue study drug during the Open Label extension phase. For the purpose of scheduling a 30 Day Follow Up Visit, a ± 6 days window may be used.
e Early Study Drug Discontinuation Visit to occur within 72 hours of last dose of study drug.
f Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator).
g Symptom directed physical examination as needed
h Weight only
i Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, PT/INR, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) and PTH. At End of E/C/F/TAF Visit, Week 24 OL, and Week 48 OL analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. This sample should be drawn prior to hemodialysis. The timing of draw and timing of hemodialysis should be recorded.
j Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, 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. At End of E/C/F/TAF Visit, Week 24 OL, and Week 48 OL analyses of glucose will be done as part of fasting metabolic assessments and not as part of the chemistry profile.
k Females of childbearing potential only. FSH test is required for female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
l If the HIV 1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2 3 weeks after the date of the original test (except for screening and baseline results). See Protocol Section 6.7.3.
m HIV 1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic rebound with HIV 1 RNA value ≥ 200 copies/mL. Subjects should be managed according to the Virologic Rebound Schema (see Protocol Section 6.7.3). HIV 1 genotype/phenotype sample collection to occur if subject's HIV 1 RNA lab values meet the criteria described in this section.
n CBC with differential and platelet count
[redacted]
p At Week 4 OL, Week 24 OL and Week 48 OL study visits, on the day of hemodialysis, a sparse timed blood sample will be collected within 10 minutes before hemodialysis initiates from all subjects. Pre dose (within 30 minutes prior to study drug administration) blood draws for plasma samples will also be collected at these visits. Study drug administration will be observed. Plasma concentrations of BIC may be determined. Plasma concentrations of other analytes may also be explored.

Appendix 3. Flowchart of US FDA-defined Snapshot Algorithm for Switch Trial

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



* On-treatment values include 1) data collected up to 1 day after the last dose date for subjects who prematurely discontinued or completed study drug or 2) all the data for subjects who were ongoing

Appendix 4. Cardiovascular or Cerebrovascular Events

An adverse event record will be flagged as a cardiovascular or cerebrovascular event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following 3 SMQs under MedDRA v22.0 provided by Gilead PVE (search name: Ischemic cardiac and cerebral events narrow) and reviewed by Gilead medical monitors.

	SMQ Source
Cardiovascular or Cerebrovascular Events	Ischaemic central nervous system vascular conditions (SMQ) – Narrow Scope Term
	Myocardial infarction (SMQ) - Narrow Scope Term
	Other ischaemic heart disease (SMQ) - Narrow Scope Term

Appendix 5. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT is included in this pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA v22.0 provided by Gilead PVE (search name: Non-infectious, non-congenital hepatobiliary disorders) and reviewed by Gilead medical monitors.

	SMQ Source
Hepatic Events (HEP)	Biliary neoplasms benign (incl cysts and polyps) (SMQ)
	Biliary malignant tumours (SMQ)
	Biliary tumours of unspecified malignancy (SMQ)
	Biliary system related investigations, signs and symptoms (SMQ)
	Biliary tract disorders (SMQ)
	Gallbladder related disorders (SMQ)
	Gallstone related disorders (SMQ)
	Cholestasis and jaundice of hepatic origin (SMQ)
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
	Hepatitis, non-infectious (SMQ)
	Liver neoplasms, benign (incl cysts and polyps) (SMQ)
	Liver malignant tumours (SMQ)
	Liver tumours of unspecified malignancy (SMQ)
	Liver related investigations, signs and symptoms (SMQ)
	Liver-related coagulation and bleeding disturbances (SMQ)

Appendix 6. TFL Mocks

Appendix Table 1. Subject Disposition, All Screened Subjects

Visit	GEN
Subjects Screened	75
Screen Failure Subjects Who Were Not Enrolled	15
Subjects Met All Eligibility Criteria and Not Enrolled*	5
Subjects Enrolled	55
Subjects Enrolled and Never Treated	0
Subjects in E/C/F/TAF Safety Analysis Set	55
Subjects in E/C/F/TAF Full Analysis Set	55
Subjects Completing E/C/F/TAF Study Treatment	xx (xx.x%)
Subjects Prematurely Discontinuing E/C/F/TAF Study Treatment	xx (xx.x%)
Reasons for Prematurely Discontinuing E/C/F/TAF Study Treatment	
Reason 1	xx (xx.x%)
Reason 2	xx (xx.x%)
Reason x	xx (xx.x%)
Subjects Enrolling in B/F/TAF Open Label Extension Phase	xx
Subjects in B/F/TAF Safety Analysis Set	xx
Subjects in B/F/TAF Full Analysis Set	xx
Subjects Completing B/F/TAF Study Treatment	xx (xx.x%)
Subjects Prematurely Discontinuing B/F/TAF Study Treatment	xx (xx.x%)
Reasons for Prematurely Discontinuing B/F/TAF Study Treatment	
Reason 1	xx (xx.x%)
Reason 2	xx (xx.x%)
Reason x	xx (xx.x%)
Subjects Completing Study	xx (xx.x%)
Subjects Prematurely Discontinuing from Study	xx (xx.x%)
Reasons for Prematurely Discontinuing from Study	
Reason 1	xx (xx.x%)
Reason 2	xx (xx.x%)
Reason x	xx (xx.x%)

The denominator for percentages of subjects is the number of subjects in the E/C/F/TAF Safety Analysis Set except for the categories related to the B/F/TAF Open Label Extension Phase for which the denominator is the number of subjects in the B/F/TAF Safety Analysis Set.
The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials.
* Among 5 subjects who met all eligibility criteria but were not enrolled, the reasons (N) were: withdrew consent (4) and outside of visit window (1).

Appendix Table 2. Virologic Outcome at Week 96 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm), Full Analysis Set

	GEN (N = xxx)
HIV-1 RNA < 50 copies/mL	xx (xx.x%)
95% CI	xx.x% to xx.x%
HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)
95% CI	xx.x% to xx.x%
HIV-1 RNA ≥ 50 copies/mL in Week 96 Window	xx (xx.x%)
Discontinued Study Drug Due to Lack of Efficacy	xx (xx.x%)
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)
No Virologic Data in Week 48 Window	xx (xx.x%)
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	xx (xx.x%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	xx (xx.x%)
Missing Data During Window but on Study Drug	xx (xx.x%)

Week 96 window is between Day 631 and 714 (inclusive).
* Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Appendix Table 3. Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit, Missing Excluded

	GEN (N = xx)
HIV-1 RNA at Week XX	
< 50 copies/mL	
95% CI	
< 20 copies/mL	
< 20 copies/mL Not Detectable	
< 20 copies/mL Detectable	
20 to < 50 copies/mL	
≥ 50 copies/mL	

The denominator for percentages is the number of subjects in the E/C/F/TAF Full Analysis Set.
The 95% CI for percentage estimate of HIV 1 RNA < 50 copies/mL was obtained using Exact method.

Appendix Table 4. Liver-Related Laboratory Test Abnormalities

	GEN (N = xx)
AST	
> 3 x ULN	xx/xx (xx.x%)
> 5 x ULN	xx/xx (xx.x%)
> 10 x ULN	xx/xx (xx.x%)
> 20 x ULN	xx/xx (xx.x%)
ALT	
> 3 x ULN	xx/xx (xx.x%)
> 5 x ULN	xx/xx (xx.x%)
> 10 x ULN	xx/xx (xx.x%)
> 20 x ULN	xx/xx (xx.x%)
AST or ALT	
> 3 x ULN	xx/xx (xx.x%)
> 5 x ULN	xx/xx (xx.x%)
> 10 x ULN	xx/xx (xx.x%)
> 20 x ULN	xx/xx (xx.x%)
Total Bilirubin	
> 1 x ULN	xx/xx (xx.x%)
> 2 x ULN	xx/xx (xx.x%)
Alkaline Phosphatase (ALP)	
> 1.5 x ULN	xx/xx (xx.x%)

	GEN (N = xx)
AST or ALT > 3 x ULN	xx/xx (xx.x%)
Total Bilirubin > 1.5 x ULN	xx/xx (xx.x%)
Total Bilirubin > 2 x ULN	xx/xx (xx.x%)
Total Bilirubin > 2 x ULN and ALP < 2 x ULN	xx/xx (xx.x%)

ULN upper limit of normal.
Denominator for percentage for individual test is the number of subjects in the E/C/F/TAF Safety Analysis Set with at least 1 postbaseline laboratory value.
The most severe postbaseline value per subject was summarized for each laboratory test. For AST, ALT, AST or ALT, and total bilirubin, subjects may be counted in multiple categories, eg, subject would be counted in > 3 ULN, > 5 ULN and > 10 ULN if the worst value was > 10 ULN.
For the composite endpoint of AST or ALT, and total bilirubin with or without alkaline phosphatase (ALP), subjects were counted once when the criteria were met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis set with nonmissing postbaseline values of the tests in evaluation at the same postbaseline visit date.

Appendix Table 5. Individual Data and Summary Statistics of Plasma Bictegravir Concentration (ng/mL) at Protocol-Specified Sampling Times

Subject ID	Week 4 Sparse	Week 4 Predose	Week 24 Sparse	Week 24 Predose	Week 48 Sparse	Week 48 Predose
#####-####						
#####-####						
N Mean SD % CV						
Median Min Max						
Q1 Q3						
N (LN-scale) Geom. Mean 95% CI(L) 95% CI(U)						
# BLQ						

BLQ Below Limit of Quantitation.
Geom. Mean Geometric Mean. LN Natural log.

PPD

Appendix 7. Programming Specifications

1) AGE is calculated as follows:

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

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

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

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

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

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

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

2) All screened subjects refer to all subjects who are screened and have a screening number. For summarization, same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used for identifying unique screened subjects.

3) Screen failure subjects are the subjects who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

4) Subjects in the All Enrolled analysis set are defined as subjects enrolled into the study. IXRSENRL is the source to determine whether the subject is enrolled.

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

6) Body mass index (BMI) is calculated from height in meters (eg, height in cm/100) and weight in kilograms as:

   - BMI will be calculated at baseline. Baseline height and weight will be used for the Calculation: Height will be obtained from *Vital Signs Performed eCRF* at screening visit; Weight will be obtained from *Vital Signs Performed eCRF* at the baseline visit; if it is missing, Weight at the screening visit from *Vital Signs Performed eCRF* will be used. For B/F/TAF baseline, the last nonmissing Weight value obtained on or prior to the date of first B/F/TAF study drug will be used.

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

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

   Subjects with Race "Not Permitted" will also be excluded to define Race subgroup (ie, black vs. nonblack) for efficacy subgroup analysis.

8) Baseline disease characteristics

   Baseline disease characteristics in Section 5.2 will be summarized for both the E/C/F/TAF Safety Analysis Set and the B/F/TAF Safety Analysis Set. Baseline disease characteristics collected at enrollment include mode of infection, HIV disease status, HCV antibody status, medical history (including Type I or II diabetes, cardiovascular disease, hypertension, hyperlipidemia), smoking status, duration of hemodialysis, and pre-switch ARVs. These characteristics are defined prior to the first dose of E/C/F/TAF.

   The following baseline characteristics will be re-defined for the B/F/TAF summary:

   - HIV-1 RNA categories (copies/mL): (a) < 50 and (b) ≥ 50
   - CD4 cell count (/μL)
   - CD4 cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
   - CD4%
   - $eGFR_{CG}$ (mL/min)

9) Medical history of interest at study entry

   Medical history of diabetes, hypertension, cardiovascular disease, and hyperlipidemia will be summarized at study entry (E/C/F/TAF baseline) as baseline disease characteristics. A subject who had medical history of one of these diseases is a subject who experienced at least one selected medical history reported in the Medical History eCRF, including keywords as below.

Hypertension	Diabetes	Cardiovascular Disease	Hyperlipidemia
HYPERTENSION	DIABETES	CEREBRAL VASCULAR ACCIDENT	HYPERLIPIDEMIA
HIGH BLOOD PRESSURE	DIABETIC	CEREBROVASCULAR ACCIDENT	DYSLIPIDEMIA
		MYOCARDIAL INFARCTION	HYPERCHOLESTEREMIA
		CONGESTIVE HEART FAILURE	HYPERCHOLESTEROLEMIA
		CORONARY ARTERY DISEASE	HIGH CHOLESTEROL
		CORONARY ARTERY CALCIFICATION	HIGH TRIGLYCERIDES
		PERIPHERAL VASCULAR DISEASE	ELEVATED CHOLESTEROL
		CARDIOMYOPATHY	HYPERGLYCERIDAEMIA
		HEART DISEASE	
		TRANSIENT ESCHEMIC ATTACK	
		AGINA	
		ARTERY BLOCKAGE	
		CARDIOVASCULAR DISEASE	

In addition, subject who experienced hypertension before starting study drug according to Adverse Event eCRF with reported term includes the key word “HYPERTENSION”.

10) To calculate years on hemodialysis at study entry, please use the Medical History CRF to find the earliest (according to MH start date on Medical History CRF) hemodialysis medical record containing any of the following keywords:

a) “ESRD”

b) “END” + “STAGE” + “RENAL”/“KIDNEY” + “DISEASE”/“FAILURE”

c) “RENAL”/“KIDNEY”/“HEMO” + “DIALYSIS”

d) “RENAL”/“KIDNEY” + “DISEASE”/“FAILURE” + “SEVERE”/“STAGE_VI”

For each subject, year on HD year of first E/C/F/TAF dose date start year of the hemodialysis medical record captured as above + 1.

11) Smoking status at study entry

Smoking status at baseline (ie, never smoked, former smoker, and current smoker) will be summarized as part of the baseline disease characteristics.

Former smoker at baseline refers to the subjects who have stopped the use of any Cigarettes or Cigars before study day 1 (ie, the first E/C/F/TAF dose date).

Current Smoker at baseline refers to the smokers who have used any Cigarettes or Cigars at study day 1.

Never smoker at baseline refers to subjects who have no record with Type of Substance Use "Cigarettes" or "Cigars" on or prior to study day 1.

How to classify a subject as never smoker, former smoker, or current smoker at baseline is specified as follows:

a) First select only records with *Type of Substance Use* "Cigarettes" or "Cigars". Records with *Type of Substance Use* "Other" (including chew tobacco, e-cigarettes, etc) will not be considered as smoking.

b) Second, for each selected substance use record, flag whether it is "Prior", "Present", or "Post" relative to the first E/C/F/TAF dose date according to the algorithm below.

c) Finally, (1) the subject will be flagged as "Never" smoker, if the subject has no record with *Type of Substance Use* "Cigarettes" or "Cigars" or all selected records have a flag of "Post"; (2) the subject will be flagged as a "Former" smoker, if any selected record has flag of "Prior" and no record of "Present"; (3) Otherwise, the subject will be flagged as a "Current" smoker, if any selected records has a flag of "Present".

	Selected Substance Use Records							
Prior	No	No	Yes	Yes	Yes	No	No	Yes
Present	No	No	No	No	Yes	Yes	Yes	Yes
Post	No	Yes	No	Yes	No	No	Yes	Yes
Smoking Status	Never	Never	Former	Former	Current	Current	Current	Current

Algorithm to flag whether a selected record is "Prior", "Present", or "Post" relative to the first E/C/F/TAF dose date:

a) The start and stop dates of the selected record are not completely missing (ie, at least year is known) or the start date is not missing and record is ongoing. The complete start or stop dates will be used to compare with the first dose date whenever possible. Otherwise, the month and year (or year alone if month is not recorded) of the start or stop dates will be used to compare with the first dose date when the start or stop date of the selected record is incomplete:

   i) The record is flagged as "Prior", if the stop date is before the first dose date;

   ii) The record is flagged as "Present", if the start date is on or before the first dose date and the stop date is on or after the first dose date, or the selected record is marked as ongoing and the start date is on or before the first dose date;

   iii) The record is flagged as "Post", if the start date is after the first dose date

b) The start date of the selected record is completely missing. We assume that the start date is before the first dose date, the stop date (or the month and/or year of the stop date, if stop date is incomplete) or "ongoing" will be used to determine whether the selected record is "Prior" or "Present" as follows:

   i) The record is flagged as "Prior", if the stop date is before the first dose date or the stop date is completed missing and the record is not marked as ongoing.

   ii) The record is flagged as "Present", if the stop date is on or after the first dose date or the selected record is marked as ongoing.

c) The start date of the selected record is before the first dose date, but the stop date is completely missing and the record is not marked as ongoing. We assume that the end date is before the first dose date, the record is flagged as "Prior".

d) The start date of the selected record is on or after the first dose date, but the stop date is completely missing and the record is not marked as ongoing. This is a data issue, should be queried first. However, this record is flagged as "Present" if the start date is on the first dose; this record is flagged as "Post" if the start date is after the first dose.

12) Clarification for defining Pre-ARV Categories.

Subjects are grouped by the pre-ARV at baseline (pre-switch). Pre-switch ARVs include ARVs that the subject was receiving 1 or 2 days before the first dose date. For each subject, classify them in each ARV category per Appendix Table 6.

Appendix Table 6. ARV Category

Pre-ARV Categories	CMTRT3	ABBR	INGRED
TDF containing ARV	NRTI/INI: Stribild (EVG+COBI+FTC+TDF)	STB	EVG COBI FTC TDF
	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATR	EFV FTC TDF
	NRTI/NNRTI: Complera (FTC+RPV+TDF)	CPA	FTC RPV TDF
	NRTI: Tenofovir DF (TDF)	TDF	TDF
	NRTI: Truvada (FTC+TDF)	TVD	FTC TDF
COBI/RTV/RPV containing ARV	NRTI/INI: Stribild (EVG+COBI+FTC+TDF)	STB	EVG COBI FTC TDF
	NRTI/NNRTI: Complera (FTC+RPV+TDF)	CPA	FTC RPV TDF
	NNRTI: Rilpivirine (RPV)	RPV	RPV
	PI: Kaletra (LPV+RTV)	LPV/r	LPV RTV
	PI: Ritonavir (RTV)	RTV	RTV
	Other	COBI	COBI
ABC containing ARV	NRTI: Abacavir (ABC)	ABC	ABC
	NRTI: Epzicom/Kivexa (ABC+3TC)	EPZ	ABC 3TC
	NRTI: Trizivir (ABC+AZT+3TC)	TZV	ABC AZT 3TC
FTC containing ARV	NRTI/INI: Stribild (EVG+COBI+FTC+TDF)	STB	EVG COBI FTC TDF
	NRTI/INI: Genvoya (EVG+COBI+FTC+TAF)	E-C-F-TAF	EVG COBI FTC TAF
	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATR	EFV FTC TDF
	NRTI/NNRTI: Complera (FTC+RPV+TDF)	CPA	FTC RPV TDF
	NRTI: Emtricitabine (FTC)	FTC	FTC
	NRTI: Truvada (FTC+TDF)	TVD	FTC TDF
3TC containing ARV	NRTI: Lamivudine (3TC)	3TC	3TC
	NRTI: Epzicom/Kivexa (ABC+3TC)	EPZ	ABC 3TC
	NRTI: Trizivir (ABC+AZT+3TC)	TZV	ABC AZT 3TC
	NRTI: Combivir (AZT+3TC)	CBV	AZT 3TC
FTC containing ARV	NRTI/INI: Stribild (EVG+COBI+FTC+TDF)	STB	EVG COBI FTC TDF

13) Last Dose Dates and Last Study Date:

a) Last Dose Date is defined in SAP Section 3.8.1. If the last dose date is incomplete or missing, the last dose date will be imputed as follows, using E/C/F/TAF or B/F/TAF dosing information as appropriate:

- If the last dose date is missing day (ie, month and year of the last dose are known), the latest of dispensing dates of study drug bottles, study drug start dates and end dates, and imputed last dose date (day imputed as 15) will be used to impute the last dose date. However, if the month of the dispensing date is after the month of the last dose date, data query is needed. If subject died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

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

b) Last Study Date is the maximum of nonmissing study drug start dates and end dates, clinic visit and laboratory visit dates, including the 30-day follow-up visit date for subjects who prematurely discontinued study or who completed study according to study completion eCRF. Please note: if study drug start date or end date is partially missing, the imputed date (day imputed as 15) will be used. If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date. Note that last visit date and last lab date include the 30-day follow-up visit.

14) Toxicity Grades:

a) With regards to Triglycerides and Hypercholesterolemia, if the fasting status is not ‘Y’, in other words it is blank or ‘N’, then the lab result value would not be graded as non-fasting values are not interpretable.

b) For toxicity grade summary, we will include all postbaseline graded results up to 30 days after the last dose of study drug, not just those at summarized visits.

15) Clarification of the following LOCF algorithms:

- Baseline values will not be carried forward.

- For CD4: If a value is missing in an analysis visit window, replace the missing value with the last on- treatment value observed before the analysis visit window that has the missing value.

16) For safety ECGs at postbaseline visits, the most conservative (worst) value within the window will be selected, eg, abnormal will be selected over normal for safety ECG or clinically significant abnormal will be selected over not clinically significant normal if there are multiple abnormal findings.

17) Treatment-Emergent Adverse Events

Events with Missing Onset Day and/or Month

The event is treatment emergent for the E/C/F/TAF phase if the following 3 criteria are met:

- The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of E/C/F/TAF study drug, and
- The month and year (or year) of the onset date is the same as or before the month and year (or year) of the date corresponding to the minimum of (1) the last dose of E/C/F/TAF study drug plus 30 days AND (2) the first dose of B/F/TAF study drug minus 1 day, and
- End date is as follows:

  The (complete) end date is on or after the first E/C/F/TAF dose date, or

  The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of E/C/F/TAF study drug, or

  End date is completely missing

The event is treatment emergent for the B/F/TAF OL extension phase if the following 3 criteria are met:

- The month and year (or year) of onset date is after the month and year (or year) of the first dose of B/F/TAF study drug, and
- The month and year (or year) of the onset date is the same as or before the month and year (or year) of the date corresponding to the last dose of B/F/TAF study drug plus 30 days, and
- End date is as follows:

  The (complete) end date is on or after the first B/F/TAF dose date, or

  The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of B/F/TAF study drug, or

  End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE for the E/C/F/TAF phase if end date is as follows:

- The (complete) end date is on or after the first E/C/F/TAF dose date, or
- The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of E/C/F/TAF study drug, or
- End date is completely missing

18) Calculation of ratios

To calculate laboratory ratios (eg, fasting total cholesterol to HDL ratio), lab value of each test in the ratio needs to be from the same accession number; if any test value used for the ratio calculation from the same accession number is missing, the ratio is not calculable (ie, missing).

19) Graded Laboratory Abnormalities Summary

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

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)

20) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 8.6.2)

21) Lipid modifying medication analyses:

- Lipid modifying medication is defined to be the concomitant medication with ACLAS "LIPID MODIFYING AGENTS" and CMDECOD contains wording of "STATIN" in the ADCM dataset.

- Subjects who took lipid modifying medications at study entry refer to the subjects who have any use of the lipid modifying agents at study day 1 (ie, the first E/C/F/TAF dose date).

  a) More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in E/C/F/TAF Safety Analysis set meeting both the following criteria: 1) any selected CM record with the start date ≤ the first E/C/F/TAF dose date, and 2) the end date of the selected CM record ≥ the first E/C/F/TAF dose date or the end date of the selected CM record is ongoing

  b) For lipid modifying medications with the start date completely unknown, we assume the start date is on or before the E/C/F/TAF first dose date, lipid modifying medication was considered as being taken at study entry if the end date is not prior to the first E/C/F/TAF dose date (ie, the end date is on or after the first E/C/F/TAF dose date, completely unknown, or ongoing).

c) Lipid modifying medications with the start date prior to the first E/C/F/TAF dose date and the end date unknown (completely missing) were considered as being taken at study entry (the unknown end date is assumed on or after the first E/C/F/TAF dose date).

- Subjects who initiated lipid modifying medications during the E/C/F/TAF phase refers to the subjects in the E/C/F/TAF Safety Analysis set who did not take lipid modifying medications at study entry and met the following criteria: 1) any selected CM record started after the first E/C/F/TAF dose date and on and prior to the last E/C/F/TAF dose date.

- Subjects who took lipid modifying medications at the start of the B/F/TAF OL extension phase refer to the subjects who have any use of the lipid modifying agents at B/F/TAF Study Day 1 (ie, the first B/F/TAF dose date).

  d) More specifically, subjects with "Lipid Modifying Agent Use at Entry in B/F/TAF OL Extension Phase" include those subjects in the B/F/TAF Safety Analysis set meeting both the following criteria: 1) any selected CM record with the start date ≤ the first B/F/TAF dose date, and 2) the end date of the selected CM record ≥ the first B/F/TAF dose date or the end date of the selected CM record is ongoing

  e) For lipid modifying medications with the start date completely unknown, we assume the start date is on or before the B/F/TAF first dose date, lipid modifying medication was considered as being taken at start of B/F/TAF OL extension phase if the end date is not prior to the first B/F/TAF dose date (ie, the end date is on or after the first B/F/TAF dose date, completely unknown, or ongoing).

  f) Lipid modifying medications with the start date prior to the first B/F/TAF dose date and the end date unknown (completely missing) were considered as being taken at the start of the B/F/TAF OL extension phase (the unknown end date is assumed on or after the first B/F/TAF dose date).

- Subjects who initiated lipid modifying medications during the B/F/TAF OL extension phase refers to the subjects in the B/F/TAF Safety Analysis set who did not take lipid modifying medications at the start of the B/F/TAF OL extension phase and met the following criteria: 1) any selected CM record started after the first B/F/TAF dose date and on and prior to the last B/F/TAF dose date.

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

23) LDL: Conversions between 2nd and 3rd generations

LDL was analyzed by 2 different assays in the study: 2nd generation (RCT2394) and 3rd generation (RCT3870). Samples collected at earlier visits were analyzed using LDL 2nd generation assay. Samples collected at later visits were analyzed using LDL 3rd generation assay. The conversion formulas are as follow:

2nd Gen (mmol/L) (3rd Gen - 0.0626)/0.882

3rd Gen (mmol/L) (0.882 x 2nd Gen) + 0.0626

For this analysis, since LDL samples were analyzed by 2nd generation assay at Baseline, only conversion from 3rd generation to 2nd generation will be performed.

For the analysis of change from baseline in fasting direct LDL: the sample analyzed by LDL 3rd generation assay will be converted to 2nd generation as a new record with test codes of LIP.LDL.00.02 in raw data. During ADaM stage, a derived parameter code (FLDL2) for "Fasting LDL Cholesterol 2ND GEN Combined" will be generated to pool the records from both original and converted (LIP.LDL.00.02) 2nd generation results to calculate the change from baseline in fasting direct LDL.

For the analysis of toxicity grade for fasting direct LDL: toxicity grade will be based on the Gilead grading results (ie, toxgrg) from the original values before conversion. In another words, during ADaM programming stage, a derived parameter code (FLDLTOX) for "Fasting LDL Cholesterol for Toxicity" will be generated to pool the records from 2nd generation and 3rd generation to derive treatment-emergent toxicity grades, maximum postbaseline toxicity grades, etc.

24) Plasma concentrations

During the B/F/TAF OL extension phase, at Weeks 4, 24, and 48, on the day of hemodialysis, a sparse timed blood sample was to be collected from all subjects within 10 minutes prior to hemodialysis initiation. Predose (within 30 minutes prior to study drug administration) blood draws for plasma samples were also collected at these visits. For the summary table, all values will be listed; however only trough values will be included in the summary statistics. Values not included in the summary statistics should be flagged.

In general, intensive PK concentration values that are BLQ will be treated as 0 at predose timepoints and one-half the value of the LLOQ at postdose time points for summary purposes. Other PK concentration values (including trough, predose, postdose, anytime PK concentration) that are BLQ will be treated as one-half of the LLOQ.

SAP Final GS-US-292-1825

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Project Team Leader eSigned	03-Dec-2019 11:13:38
PPD	Biostatistics eSigned	03-Dec-2019 17:27:06
PPD	Project Team Leader eSigned	05-Dec-2019 01:44:24