STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and Either Emtricitabine/Tenofovir Alafenamide or Emtricitabine/Tenofovir Disoproxil Fumarate to a Fixed Dose Combination of Bictegravir/ Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected Subjects who are Virologically Suppressed
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF; GS-9883/F/TAF)
Study Number:	GS-US-380-4030
Protocol Version (Date):	Amendment 2 (28 June 2018)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	30 April 2021
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
ART	antiretroviral treatment
AST	aspartate aminotransferase
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC; F) 200 mg / tenofovir alafenamide (TAF) 25 mg
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
DC	premature study drug discontinuation
DNA	deoxyribonucleic acid
DTG	dolutegravir, tivicay
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{(CG)}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
F/TAF	fixed dose combination of emtricitabine (FTC; F)/ tenofovir alafenamide (TAF)
FTC, F	emtricitabine
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GS-9883	bictegravir
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e-antibody
HBeAg	hepatitis B e-antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL	high density lipoprotein

HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IDMC	independent data monitoring committee
INSTI	integrase strand-transfer inhibitor
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OL	open label
PP	per protocol
PT	preferred term
GLPS	global patient safety
Q	quartile
Q1	first quartile
Q3	third quartile
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TFL	tables, figures, and listings
ULN	upper limit of normal
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 final analysis for Study GS-US-380-4030, 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 dated 28 June 2018 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report.

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of dolutegravir (DTG) and emtricitabine (FTC; F) / tenofovir alafenamide (TAF) or DTG + FTC/tenofovir disoproxil fumarate (TDF) to a fixed dose combination (FDC) of bictegravir (B)/F/TAF versus DTG + F/TAF in virologically suppressed HIV-1 infected subjects with or without antiretroviral (ARV) resistance as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objective of this study is:

- To evaluate the safety and tolerability of the two treatment groups through Week 48

1.2. Study Design

Design Configuration and Subject Population

GS-US-380-4030 is a randomized, double-blinded, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of B/F/TAF tablet versus DTG + F/TAF in HIV-1 infected subjects who are virologically suppressed.

Treatment Groups

Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** FDC of B/F/TAF (50/200/25 mg) + placebo to match DTG 50 mg + placebo to match FDC of F/TAF (200/25 mg) administered orally, once daily (QD), without regard to food (total of 3 tablets) (n=260)
- **Treatment Group 2:** DTG 50 mg + FDC of F/TAF (200/25 mg) + placebo to match FDC of B/F/TAF (50/200/25 mg) administered orally, QD, without regard to food (total of 3 tablets) (n=260)

Key Eligibility Criteria

Medically stable HIV-infected subjects who meet the following criteria:

- Currently receiving an ARV regimen of DTG+F/TAF or DTG+F/TDF for the following minimum time periods:
  - ≥ 6 months (if there is documented or suspected nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance prior to the screening visit),
  - ≥ 3 months (if there is no documented or suspected NRTI resistance prior to the screening visit)
- Documented plasma HIV-1 RNA < 50 copies/mL during treatment with DTG+F/TAF or DTG+F/TDF (for a minimum period of ≥ 6 or ≥ 3 months, as applicable) preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL)
  - The last two HIV-1 RNA measurements prior to screening must be < 50 copies/mL; however, unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") in the past are acceptable.
  - If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL (eg, < 20 copies/mL), the plasma HIV-1 RNA level cannot exceed 50 copies/mL on 2 consecutive HIV-1 RNA tests after < 50 copies/mL has been achieved.
- HIV-1 RNA levels < 50 copies/mL at screening visit.
- Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$)
- No documented resistance to integrase stand-transfer inhibitors (INSTIs) or confirmed virologic failure (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving < 50 copies/mL while on an INSTI-containing regimen)
  - Eligible subjects with the following historical ARV resistance are permitted to enroll:
    - Any NRTI resistance mutations
    - Any non-nucleoside reverse transcriptase mutations
    - Any protease inhibitor mutations
    - Subjects with resistance to 2 or more classes of antiretrovirals must be reviewed by the Gilead medical monitor to confirm eligibility
- Eligible subjects with chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection are permitted to enroll

Study Periods / Phases

Subjects will be treated for at least 48 weeks during the blinded treatment phase.

After Week 48, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 48 Visit and Week 48 analysis is completed, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open-label (OL) extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

All subjects participating in the OL extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter for up to 96 weeks.

Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the open-label B/F/TAF FDC extension phase, will be required to return to the clinic 30 days after the End of Blinded Treatment Visit for a 30-Day Follow-Up Visit.

Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for at least 48 weeks. Following the Day 1 Visit, subjects will return for study visits at Weeks 4, 8, and 12, and then every 12 weeks through the End of Blinded Treatment Visit.

For all eligible subjects, blood and urine will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the End of Blinded Treatment Visit. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count and percentage, and complete or symptom-directed physical examinations will be performed at the Screening, Day 1, and all subsequent study visits.

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

Historical HIV-1 RNA genotypes (from resistance testing) will be collected, if available.

More details for study procedure could be found in Appendix 1.

Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups
(Treatment Group 1: Treatment Group 2). Randomization will be stratified by prior NRTI use (F/TAF vs. F/TDF) and documented or suspected history of NRTI resistance.

NRTI resistance will be stratified by the following categories:

1) K65R/E/N, or 3 or more thymidine analogue mutations (TAMs) that include M41L or L210W, or T69 insertions (TAMs are: M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N)

2) Any other pattern of NRTI resistance of M41L, D67N, K70R, L74I/V, Y115F, Q151M, M184I/V, L210W, T215F/Y, K219Q/E/R/N, T69D, K70E/G/M/Q/S/T, V75A/S/M/T

3) None of these mutations/no NRTI resistance

Site and/or Stratum Enrollment Limits

Approximately 100 study sites in North America and Europe. There was no enrollment limit for individual sites.

Study Duration

The randomized, double-blind phase of this study is at least 48 weeks in duration. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open-label (OL) extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

1.3. Sample Size and Power

A total of approximately 520 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (260 subjects per treatment group), achieves at least 90% power to detect a non-inferiority margin of 4% in difference in percentage of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups.

For sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (based on the historical Gilead Genvoya® and Stribild® studies), that a non-inferiority margin is 4%, and that the significance level of the test is at a one-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

1.4. Actual Sample Size and Power

It was noted that the unconditional exact method using 2 inverted 1-sided tests is more appropriate than normal approximation method that was used for the sample size calculation in the protocol due to the fact that the proportion of participants with HIV-1 RNA ≥ 50 copies/mL was very low. Using PASS 14 software, the actual power calculated based on the actual sample size of 565 was 85% power, instead of 90% power, to detect a non-inferiority margin of 4% at a one-sided alpha of 0.025 when we change the analysis from normal approximation method to exact method.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

The Week 12 Independent Data Monitoring Committee (IDMC) analysis was conducted after all subjects enrolled completed their Week 12 Visit or prematurely discontinued the study drug. The purpose of this interim analysis was to provide the IDMC with a statistical report for review. More details are documented in the IDMC charter.

Gilead does not have a prior intent to ask the IDMC to review Week 48 results or to consider early termination of the study even if there is early evidence of favorable efficacy for B/F/TAF.

2.2. Interim Analyses

2.2.1. Week 48 Analysis

The Week 48 analysis was conducted after all subjects either completed their Week 48 Visit or prematurely discontinued from the blinded study drug. This is the primary analysis of this study.

2.3. Final Analysis

The final statistical analysis will be conducted after all subjects either complete the study or prematurely discontinue from the study. This analysis will include all data collected from the randomized and the extension phases of the study.

This statistical analysis plan describes the analysis plan for the final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final analysis will include two sets of analyses: randomized phase analysis and all B/F/TAF analysis.

Randomized Phase Analysis:

- For subjects who are never treated in the extension phase of the study including those who prematurely discontinue the blinded study drug or who complete the randomized phase and do not receive any dose of B/F/TAF in the extension phase, all available data will be included in the randomized phase analysis.

- For subjects who complete the randomized phase and receive at least 1 dose of B/F/TAF in the extension phase, the randomized phase analysis will include (1) all available adverse event (AE), concomitant medication, pregnancy, and death data collected prior to the extension phase first dose date; (2) all available other data, such as laboratory, vital sign, and electrocardiogram (ECG), collected on or prior to the extension phase first dose date.

All B/F/TAF Analysis:

- For subjects who receive B/F/TAF in the randomized phase, all available data collected from both randomized phase and OL extension phase (if applicable) will be included in the all B/F/TAF analysis.

- For subjects who receive DTG + F/TAF in the randomized phase and receive at least 1 dose of B/F/TAF in the extension phase, (1) all available AE, concomitant medication, pregnancy, and death data with start date **on or after** the first dose date of B/F/TAF in the extension phase and (2) all available other data, such as laboratory, vital sign, and ECG data, collected **after** the first dose date of B/F/TAF in the extension phase will be included, except that the data collected **on or prior to** the first dose date of B/F/TAF will be used to derive the baseline value for the all B/F/TAF analysis.

Note that all data for subjects who receive DTG + F/TAF in the randomized phase and do not receive any dose of B/F/TAF in the extension phase will be excluded from all B/F/TAF analysis. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

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.

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

By-subject listings will be presented for all subjects in the All Randomized analysis set unless otherwise specified, and sorted by subject identification (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. The treatment group to which subjects were randomized will be used in the listings.

In general, age (in years) on the date of the first dose of study drug for each analysis (see Appendix 7 for details) will be used for analyses and presentation in listings. For randomized but never dosed subjects, age on the date of randomization will be used. For screen failures, age on the date of 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 the blinded study drug refers to premature discontinuation of the blinded study drug or completion of the blinded study drug. Similarly, permanent discontinuation of the extension phase study drug refers to premature discontinuation of the extension phase study drug or completion of the extension phase study drug. More specifically, for the randomized phase analysis, study drug refers to the blinded study drugs (B/F/TAF or DTG + F/TAF); for all B/F/TAF analysis, study drug refers to B/F/TAF.

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. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total.

3.1.1. Analysis Sets Used for the Randomized Phase Analysis

3.1.1.1. All Randomized Analysis Set

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

3.1.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of blinded randomized study drug. Subjects will be grouped according to the treatment to which they were randomized. For the FAS, all efficacy data collected in the randomized phase, including data collected after the last dose of blinded study drug and on or prior to the first dose date of the OL study drug (if applicable), will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.1.3. Per Protocol Analysis Set

The Week 48 **Per Protocol (PP) Analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of blinded randomized study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received. For the PP analysis, efficacy data up to 1 day after permanent discontinuation of blinded study drug will be included. The Week 48 PP analysis set is the secondary analysis set for efficacy analysis.

Subjects meeting any of the following criteria will be excluded from the Week 48 PP analysis set:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 48 analysis window, except when missing is due to discontinuation of blinded study drug for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation (DC) in the "Blinded Treatment" study phase on the study drug completion eCRF page; (Table 1).

Table 1. Subjects Excluded from Week 48 Per Protocol Analysis Set Due to Premature Discontinuation of blinded Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window

Discontinuation from blinded Study Drug prior to or on the Upper Bound of Week 48 Analysis Window		HIV-1 RNA Data on Randomized Treatment Available in Week 48 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Subjects in Week 48 PP analysis set; - = Exclusion of Subjects in Week 48 PP analysis set.

- Subjects who do not meet the inclusion criterion of receiving a stable antiretroviral regimen of DTG + F/TAF or DTG + F/TDF for the following duration prior to the screening visit:1) ≥ 6 months (if there is documented or suspected NRTI resistance), or 2) ≥ 3 months (if there is no documented or suspected NRTI resistance)

- Subjects who do not meet the inclusion criterion of having documented plasma HIV-1 RNA < 50 copies/mL during treatment with DTG+F/TAF or DTG+F/TDF (for a minimum period of ≥ 6 or ≥ 3 months, as applicable) preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL)

- Subjects who do not meet the inclusion criterion of having HIV RNA-1 < 50 copies/mL at the screening visit

- Subjects who do not meet the inclusion criterion of having no documented resistance to INSTIs or confirmed virologic failure (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving < 50 copies/mL while on an INSTI-containing regimen)

- Subjects who do not meet the inclusion criterion of only having the following permitted historical ARV resistance:
  1) Any NRTI resistance mutations
  2) Any non-nucleoside reverse transcriptase mutations
  3) Any protease inhibitor mutations
  4) Subjects with resistance to 2 or more classes of antiretrovirals must be reviewed by the Gilead medical monitor to confirm eligibility
- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in Section 4.3 of the protocol including drugs not to be used with BIC, FTC, TAF and DTG
- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 48 Visit below the 2.5th percentile

3.1.1.4. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of blinded randomized study drug. Subjects will be grouped according to the treatment they actually received. This is the primary analysis set for safety analyses.

Adverse event, concomitant medication, pregnancy, and death data collected up to 30 days after permanent discontinuation of the blinded randomized study drug and prior to the first dose date of OL study drug (if applicable) will be included in the safety summaries, unless specified otherwise.

Laboratory data (eg, hematology, chemistry, and urine analysis), vital sign, ECG data collected up to 30 days after permanent discontinuation of the blinded randomized study drug and on or prior to the first dose date of OL study drug (if applicable) will be included in the safety summaries, unless specified otherwise.

3.1.2. Analysis Set Used for the All B/F/TAF Analysis

3.1.2.1. All B/F/TAF Analysis Set

The **All B/F/TAF Analysis Set** will include all subjects who (1) are randomized into the randomized phase of the study and (2) have received at least 1 dose of the B/F/TAF in the randomized phase or at least 1 dose of the B/F/TAF in the extension phase. This is the primary analysis set for the all B/F/TAF efficacy and safety analyses.

For efficacy analyses, all efficacy data collected for the all B/F/TAF analysis will be included.

For safety analyses, all safety data collected up to 30 days after permanent discontinuation of the last B/F/TAF (including randomized and open label phases) will be included in the safety summaries, unless specified otherwise.

3.2. Subject Grouping

For the randomized phase analyses using the All Randomized Analysis Set or the FAS, subjects will be grouped by the randomized treatment (labeled as B/F/TAF vs. DTG + F/TAF). For all other randomized phase analyses, subjects will be grouped by the actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

For all B/F/TAF analyses, subjects will be grouped into the following 3 groups:

- B/F/TAF group: This group includes all subjects who actually received B/F/TAF in the randomized phase of this study, regardless whether subjects receive any B/F/TAF in the extension phase or not.
- DTG + F/TAF to B/F/TAF group: This group includes all subjects who actually received DTG + F/TAF regimen in the randomized phase of this study and then receive at least 1 dose of B/F/TAF in the extension phase
- All B/F/TAF group: This group includes all subjects who actually received at least 1 dose of B/F/TAF in either phase. This group includes the B/F/TAF group and the DTG + F/TAF to B/F/TAF group. Only data collected on and after the first dose date of B/F/TAF may be included.

Treatment comparisons will only be made between B/F/TAF and DTG + F/TAF for the randomized phase analysis.

3.3. Strata and Covariates

Randomization was stratified by prior NRTI backbone use (F/TAF vs. F/TDF) and documented or suspected history of NRTI resistance. For analysis, the baseline NRTI resistance stratum was re-classified based on virology data collected at both screening and/or baseline:

Baseline NRTI resistance stratum are as follows:

1) No NRTI mutation:

   None of these following mutations/no NRTI resistance

2) K65R/E/N or ≥ 3 TAMs:

   K65R/E/N or ≥ 3 TAMs that include M41L, L210W, or T69 insertions: K65R/E/N, or 3 or more thymidine analogue mutations (TAMs) that include M41L or L210W, or T69 insertions, (TAMs are: M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N)

3) Any other pattern of NRTI mutation:

   Any other pattern of NRTI resistance of M41L, D67N, K70R, L74I/V, Y115F, Q151M, M184I/V, L210W, T215F/Y, K219Q/E/R/N, T69D, K70E/G/M/Q/S/T, V75A/S/M/T

3.4. Examination of Subject Subgroups

Subject subgroup analysis will only be performed for randomized phase analysis unless specified below.

3.4.1. Subject Subgroups for Efficacy Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 will be analyzed for the following subject subgroups (also see Section 6.1.2.2.2 for details):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Region: (a) US and (b) Ex-US
- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 48 Visit)
- Baseline NRTI resistance (determined based on virology data): (a) No NRTI mutation (b) any NRTI mutation
- Baseline NRTI resistance (determined based on virology data): (a) No NRTI mutation, (b) K65R/E/N or ≥ 3 TAMs (c) any other pattern of NRTI mutation
- Baseline M184I/V resistance (determined based on virology data): (a) No M184I/V mutation (b) any M184I/V mutation

The proportion of subjects with HBV Deoxyribonucleic Acid (DNA) < 29 IU/mL at baseline and Week 48 and the change from baseline in $\log_{10}$ HBV DNA by visit will be analyzed for the following subject subgroup:

- Subjects with HIV/HBV coinfection at baseline

3.4.2. Subject Subgroups for Safety Analyses

1) Incidence of all treatment-emergent AEs (TEAEs) will be analyzed for the following subject subgroups (also see Section 7.1.6):
   - Age (years): (a) < 50 and (b) ≥ 50
   - Sex: (a) male and (b) female
   - Race: (a) black and (b) nonblack
   - Region: (a) US and (b) Ex-US
2) Renal-related laboratory tests (ie, serum creatinine and $eGFR_{CG}$) and fasting metabolic laboratory tests will be analyzed for each subgroup of baseline NRTI backbone: (a) F/TAF (b) F/TDF

3) Selected safety endpoints may be analyzed for the following subject subgroups for randomized phase analysis and for all B/F/TAF analyses (see Section 8.1 for details):

   - Subjects with HIV/HBV coinfection at baseline
   - Subjects with incident HIV/HBV coinfection while on study drug (if any)

4) Selected safety endpoints will be analyzed for the following subject subgroups for randomized phase analysis and for all B/F/TAF analyses (see Section 8.2 for details):

   - Subjects with HIV/HCV coinfection at baseline
   - Subjects with incident HIV/HCV coinfection while on study drug (if any)

3.5. Multiple Comparisons

The noninferiority evaluation of the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 was the prespecified primary comparison. However, 1 interim IDMC analysis was performed prior to the analysis for the primary endpoint and an alpha penalty of 0.00001 was applied. Therefore, the alpha level for the primary endpoint (ie, the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48) was adjusted to 0.04999 (corresponding to 95.001% confidence interval [CI]) using both the FAS and the Week 48 PP analysis set. The alpha level for the key secondary efficacy endpoint, the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, will be also adjusted to 0.04999 (corresponding to 95.001% CI) to be conservative.

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 prematurely 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 dosing 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 7.1.5.2, and for concomitant non-ARV medications in Section 7.4.2.

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 are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows except for urine creatinine:

- 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).

Logarithmic (base 10) transformations will be applied to HIV-1 RNA and HBV DNA 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. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purposes. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purposes.

3.8. Analysis Windows

3.8.1. Definition of Study Day

Study Day 1 for the Randomized Phase analysis is defined as the day when the first dose of blinded randomized study drug (ie, B/F/TAF or Placebo, or DTG or Placebo, or F/TAF or Placebo) was taken, as recorded on the Study Drug Administration eCRF for "Randomized Phase".

Last Dose Date for the Randomized Phase analysis is the latest of the blinded randomized study drug (ie, B/F/TAF or Placebo, or DTG or Placebo, or F/TAF or Placebo) end dates recorded on the Study Drug Administration eCRF for "Randomized Phase".

If the last dose date for the randomized phase analysis is missing (eg, only year of last dose is known or completely missing due to lost to follow-up), the latest of the blinded study drug start dates and end dates, or the latest of clinical and the laboratory visit dates prior to the first dose date of B/F/TAF in the extension phase (if applicable), excluding the 30-day follow-up visit date, will be used to impute the last dose date. For other partial missing last dose date, please see the Appendix 7 for imputation rule details.

Study Day 1 for the all B/F/TAF analysis is defined as

- For subjects who actually received B/F/TAF in the randomized phase of this study (ie, B/F/TAF group), **Study Day 1** for the all B/F/TAF analysis is defined as the day when the first dose of B/F/TAF in the randomized phase was taken, as recorded on the Study Drug Administration eCRF form.

- For subjects who actually received DTG + F/TAF in the randomized phase of this study and then receive at least 1 dose of B/F/TAF in the extension phase (ie, DTG + F/TAF to B/F/TAF group), **Study Day 1** for the all B/F/TAF analysis is defined as the day when the first dose of B/F/TAF in the extension phase was taken (ie, OL B/F/TAF), as recorded on the Study Drug Administration eCRF form.

Last Dose Date for the All B/F/TAF Analysis is the latest of B/F/TAF (including both randomized phase and open label phase) end dates recorded on the Study Drug Administration eCRF form.

If the last dose date for the all B/F/TAF analysis is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up), the latest of the B/F/TAF (including both randomized phase and open label phase) start dates and end dates, the latest clinical and laboratory visit dates, excluding the 30-day follow-up visit date, will be used to impute the last dose date.

Study Days are calculated relative to Study Day 1 for the randomized phase analysis. For events that occurred on or after the Study Day 1 date, study days are calculated as (visit date minus Study Day 1 plus 1). For events that occurred prior to Study Day 1 for either analysis, study days are calculated as (visit date minus Study Day 1).

Last Study Date is the latest of the study drug (including DTG + F/TAF, and B/F/TAF in both randomized phase and open label phase) start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date.

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1 for the randomized phase analysis or the all B/F/TAF analysis, as appropriate. Subjects who actually received DTG + F/TAF in the randomized phase and received at least 1 dose of B/F/TAF in extension phase will have a baseline for Randomized Phase Analysis and a new baseline value for the all B/F/TAF analysis.

3.8.2. Analysis Windows

Subject visits might not occur on protocol specified days. Therefore, for the purpose of analysis, observations will be assigned to two different analysis windows based on the following tables: the analysis windows for the randomized phase analysis are derived relative to the Study Day 1 for the randomized phase analysis, while the analysis windows for the all B/F/TAF analysis are derived relative to the Study Day 1 for the all B/F/TAF analysis.

The analysis windows for HIV-1 RNA, CD4+ cell count, CD4 %, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 2 and Table 3 for randomized phase analysis and all B/F/TAF analysis separately.

Table 2. Analysis Windows for HIV-1 RNA, CD4+ cell count, CD4 %, HBV DNA, Hematology, Chemistry, Urinalysis, and Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, and Weight for Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	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 K	K*7	(K-6)*7+1	(K+6)*7

Note: Week K is every 12 weeks after previous visit.

Table 3. Analysis Windows for HIV-1 RNA, CD4+ cell count, CD4 %, HBV DNA, Hematology, Chemistry, Urinalysis, and Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, and Weight for All B/F/TAF Analysis

	B/F/TAF Group			DTG+F/TAF to B/F/TAF		
Visit ID	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 4	28	2	42	NA	NA	NA
Week 8	56	43	70	NA	NA	NA
Week 12	84	71	126	84	2	126
Week 24	168	127	210	168	127	210
Week 36	252	211	294	252	211	294
Week 48	336	295	378	336	295	378
Week 60	420	379	462	420	379	462
Week 72	504	463	546	504	463	546
Week 84	588	547	630	588	547	630
Week 96	672	631	714	672	631	714
Week k	K*7	(K-6)*7+1	(K+6)*7	K*7	(K-6)*7+1	(K+6)*7

NA = Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase; For the DTG + F/TAF to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.
Note: Week K is every 12 weeks after previous visit.

The analysis windows for metabolic assessments (including fasting glucose and lipid panel: total cholesterol, high density lipoprotein [HDL], direct low density lipoprotein [LDL], triglycerides, and total cholesterol to HDL ratio) are presented in Table 4 and Table5 for randomized phase analysis and all B/F/TAF analysis separately.

Table 4. Analysis Windows for Metabolic Assessments for Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	420
Week 72	504	421	588
Week K	K*7	(K-12)*7+1	(K+12)*7

Note: Week K is every 24 weeks after previous visit.

Table5. Analysis Windows for Metabolic Assessments for all B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TAF to B/F/TAF		
Visit ID	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 12	84	2	126	NA	NA	NA
Week 24	168	127	252	168	2	252
Week 48	336	253	420	336	253	420
Week 72	504	421	588	504	421	588
Week 96	672	589	756	672	589	756
Week K	K*7	(K-12)*7+1	(K+12)*7	K*7	(K-12)*7+1	(K+12)*7

NA = Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase; For the DTG + F/TAF to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.
Note: Week K is every 24 weeks after previous visit.

The analysis windows for HBV Serology (including HBsAb, HBsAg, hepatitis B e-antigen [HBeAg], hepatitis B e-antibody [HBeAb], HBcAb) and HCV Serology (including HCV antibody [HCVAb]), and HCV RNA assessments are presented in Table 6 and Table 7.

Table 6. Analysis Windows for HBV and HCV Serology and HCV RNA Assessments for Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week K	K*7	(K-24)*7+1	(K+24)*7

Note: Week K is every 48 weeks after previous visit.

Table 7. Analysis Windows for HBV and HCV Serology, and HCV RNA Assessments for all B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TAF to B/F/TAF		
Visit ID	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 48	336	2	504	336	2	504
Week 96	672	505	840	672	505	840
Week K	K*7	(K-24)*7+1	(K+24)*7	K*7	(K-24)*7+1	(K+24)*7

NA = Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase; For the DTG + F/TAF to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.
Note: Week k is every 48 weeks after previous visit.

Analysis window is not defined for ECG, since there is no related summary analysis.

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

Depending on the statistical analysis method, single values are 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 one 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, then records will be chosen as follows:

- For baseline, the latest available record on or prior to the first dose date of study drug for randomized phase analysis or B/F/TAF phase analysis 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, CD4%, and HBV DNA, the record(s) collected on the latest day in the window will be selected for analysis.

  — For other numeric observations (ie, except HIV-1 RNA, CD4+ cell count, CD4%, and HBV DNA), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  — For any numeric observations except HIV-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 nonmissing record on or prior to the first dose date of study drug for randomized phase analysis or B/F/TAF phase analysis 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.

- For postbaseline visits, the most conservative value within the window will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects randomized at each region, country, and investigator will be summarized by treatment group and overall using the safety analysis set. The region definition is provided in Appendix 2. The denominator for this calculation will be the number of subjects in the safety analysis set. Similarly, the number and percentage of subjects enrolled in each randomization stratum will be summarized based on reclassified strata using baseline NRTI backbone based on the Non-Study ARV Medication eCRF, and baseline NRTI resistance data as determined by Gilead Virology based on virology data instead of using interactive web response system (IWRS) data.

If there are discrepancies between IWRS and collected data with regard to stratum assignment, a listing of the discrepancies will be provided.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but never treated, subjects in the safety analysis set, subjects in the FAS.

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

- Subjects completing study drug in the double-blinded randomized phase
- Subjects prematurely discontinuing study drug in the double-blinded randomized phase (with summary of reasons for discontinuing study drug in the randomized phase)
- Subjects completing study in the double-blinded randomized phase
- Subjects prematurely discontinuing from study in the double-blinded randomized phase (with summary of reasons for discontinuing from study in the randomized phase)
- Subjects entering the OL extension phase
- Subjects treated in the OL extension phase
- Subjects completing study drug in the OL extension phase

- Prematurely discontinuing study drug in the OL extension phase (with summary of reasons for discontinuing study drug in the OL extension phase)
- Subjects completing study in the OL extension phase
- Prematurely discontinuing from study in the OL extension phase (with summary of reasons for discontinuing from study in the OL extension phase)

The denominator for the percentages of subjects in each category in the randomized phase, including "Subjects entering the OL extension phase", will be the number of subjects randomized and treated in the randomized phase. The denominator for the percentages of subjects in each category in the OL extension phase will be the number of subjects who were treated in OL extension phase.

No inferential statistics will be generated. Reasons for premature study drug/study discontinuation will be provided in by-subject listings by subject ID number in ascending order. Reasons for premature study drug/study discontinuation due to COVID-19 will also be provided in a separate listing.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined for both the randomized phase analysis and the all B/F/TAF analysis. For the randomized phase analysis, the terms "first dose date" and "last dose date" in the text below refer to the first dose date and last dose date defined for the randomized phase analysis. For the all B/F/TAF analysis, the terms "first dose date" and "last dose date" in the text below refer to the first dose date and last dose date defined for the all B/F/TAF analysis. Duration of exposure to study drug will be defined as (the last dose date – the first dose date + 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 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, eg, ≥ 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 (756days), ≥ 120 weeks (840 days), ≥ 132 weeks (924 days), ≥ 144 weeks (1008 days), ≥ 156 weeks (1092 days), ≥ 168 weeks (1176 days), etc.

Summaries will be provided by treatment group for subjects in Safety Analysis Set for the randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. No inferential statistics will be provided.

For the randomized phase analysis, time to permanent discontinuation of blinded study drug will be analyzed using the Kaplan-Meier (KM) method by treatment group based on the safety analysis set. The log rank test will be used to compare the difference in study drug exposure between the 2 treatment groups. Subjects who completed blinded randomized study drug will be censored on last blinded randomized study drug dose date. A plot of KM estimates for the time to premature discontinuation of blinded study drug by treatment group will be generated.

For all B/F/TAF analysis, time to premature discontinuation of study drug (B/F/TAF) will be analyzed by treatment group using the KM method based on the All B/F/TAF Analysis Set. No statistical comparisons will be made for the all B/F/TAF analysis. A plot of KM estimates for the time to permanent discontinuation of study drug by treatment group (B/F/TAF vs DTG + F/TAF to B/F/TAF) will be generated for the all B/F/TAF analysis. Subjects who completed study drug (B/F/TAF) will be censored at the last study drug dose date of B/F/TAF.

4.2.2. Adherence to Study Drug Regimen

Adherence to study drug regimen will be defined for both the randomized phase analysis and the all B/F/TAF analysis. For randomized phase analysis, adherence will be computed for both treatment groups, including B/F/TAF and DTG + F/TAF. For all B/F/TAF analysis, study drug adherence (B/F/TAF) will be computed for both treatment groups and overall as defined in Section 3.2. Study drug regimen adherence will be computed based on pill counts for active drug only. The numbers of pills of study drug dispensed and returned are captured on study drug accountability eCRF.

Adherence (%) of study drug regimen will be calculated as follows:

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

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

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

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

[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 for each study drug contained in the study drug regimen 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 for each study drug contained in the study drug regimen from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug 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 for that study drug will be excluded from both denominator and numerator calculation.

Overall adherence will be calculated for both the randomized phase analysis and the all B/F/TAF analysis. For the randomized analysis, overall adherence will use all data from the entire dosing period up to the last dose date of the randomized study drug. For the all B/F/TAF analysis, overall adherence will use all available data collected from both randomized phase and OL phase for subjects who actually received B/F/TAF in the randomized phase, and data on or after the first dose date of extension B/F/TAF for subjects who actually received DTG + F/TAF in the randomized phase and received at least 1 dose of B/F/TAF in the extension phase.

Descriptive statistics for adherence to study drug regimen (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for subjects who return at least 1 bottle of randomized study drug, and who have calculable adherence for the randomized phase analysis and for All B/F/TAF analysis, respectively. No inferential statistics will be provided.

4.3. Protocol Deviations

A listing will be provided for all randomized subjects who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met. A listing of subjects who received the wrong study drug will also be provided.

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

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

The determination of missing or virtual Visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 7.

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 by treatment group and overall 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 subject characteristics will be provided for subjects in Safety Analysis Set for the randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively (noticing that the baseline for all B/F/TAF analysis will be adjusted based on first dose of B/F/TAF), respectively.

For the randomized phase analysis using Safety Analysis Set, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups for categorical data, and the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups for continuous data. No statistical comparisons will be made for the all B/F/TAF analysis.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for subjects in Safety Analysis Set for the randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively:

- HIV-1 RNA categories (copies/mL): (a) < 50, (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 percentage (%)
- Mode of infection (HIV risk factors) (randomized phase analysis only)
- HIV disease status (randomized phase analysis only)
- $eGFR_{CG}$ (mL/min)
- HIV/HBV co-infection status (Yes/No/Missing, see Section 8.1 for definition)
- HIV/HCV co-infection status (Yes/No/Missing, see Section 8.2 for definition)

- Duration of baseline ARV regimen (based on the Non-Study ARV Medication eCRF): (a) DTG + F/TAF; (b) DTG + F/TDF (randomized phase analysis only)

- Baseline NRTI backbone stratum (F/TAF vs F/TDF, based on the Non-Study ARV Medication eCRF) (randomized phase analysis only)

- Baseline NRTI resistance stratum (based virology data) (a) No NRTI mutation (b) K65R/E/N or ≥ 3 TAMs (c) any other pattern of NRTI mutation (randomized phase analysis only)

For the randomized phase analysis using Safety Analysis Set, the CMH test (general association statistic for nominal data, and row means scores differ statistic for ordinal data) will be used to compare the 2 treatment groups for categorical data and the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups for continuous data.

No statistical comparisons will be made for the all B/F/TAF analysis.

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Efficacy Analysis for Randomized Phase Analysis

6.1.1. Primary Efficacy Endpoint

6.1.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purpose.

6.1.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 48 is defined as from Study Day 295 to Study Day 378, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after permanent discontinuation of study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 48 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects
  a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or
  b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and
     1) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
     2) Who discontinue study drug prior to or in the Week 48 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
     3) Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL.
- **No Virologic Data in the Week 48 Window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:
  a) Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  b) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,
  c) Missing data during the window but on study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in Appendix 2.

The Week 48 virologic outcomes for the US FDA-defined snapshot algorithm will be listed.

For switch trials, the US FDA-defined snapshot algorithm classifies subjects who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL in the "HIV-1 RNA ≥ 50 copies/mL" category. For treatment naïve study population, these subjects will be classified in the "No Virologic Data in the Week 48 Window" category.

6.1.1.3. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The B/F/TAF group (Treatment Group 1) is at least 4% higher than the DTG + F/TAF group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL (as determined by the US FDA-defined snapshot algorithm) at Week 48.

Alternative hypothesis: The B/F/TAF group (Treatment Group 1) is less than 4% higher than the DTG + F/TAF group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

6.1.1.4. Primary Analysis of the Primary Efficacy Endpoint

The analysis purpose of the primary efficacy endpoint is to assess the noninferiority of switching to B/F/TAF relative to DTG + F/TAF. Noninferiority will be assessed using a conventional 95% CI approach, with a noninferiority margin of 4%.

For the interim analysis performed for the IDMC at Week 12, an alpha of 0.00001 has been spent. Therefore, the significance level for the 2-sided test in the primary analysis at Week 48 will be 0.04999 (corresponding to 95.001% CI).

The point estimate of treatment difference (B/F/TAF group – DTG+F/TAF group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL and the associated 2-sided 95.001% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

It will be concluded that B/F/TAF is noninferior to DTG+F/TAF if the upper bound of the 2-sided 95.001% CI of the difference between treatment groups (B/F/TAF group – DTG+F/TAF group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL is less than 4%.

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 48 will be summarized.

If noninferiority of B/F/TAF versus DTG+F/TAF is established, the same 95.001% CI used in evaluating noninferiority at Week 48 will be used to evaluate superiority. If the upper bound of the 95.001% CI is less than 0, then superiority of B/F/TAF over DTG+F/TAF is established. The 2-sided Fisher's exact test will also be used to assess superiority as a secondary assessment.

The FAS will be used for the primary efficacy endpoint analysis and the superiority evaluation.

6.1.1.5. Secondary Analysis of the Primary Efficacy Endpoint

A secondary analysis based on the Week 48 PP analysis set will also be performed to evaluate the robustness of the primary analysis of the primary endpoint. For this secondary analysis, 95.001% CI for the treatment difference in the primary efficacy endpoint will also be calculated based on an unconditional exact method using 2 inverted 1-sided tests.

6.1.2. Secondary Efficacy Endpoints

6.1.2.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 48

The analyses for the secondary efficacy endpoints will be conducted using the FAS and the Week 48 PP analysis set, respectively.

6.1.2.2. Analysis of the Secondary Efficacy Endpoints

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

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 will also be analyzed by the US FDA-defined snapshot algorithm based on the FAS and Week 48 PP analysis set, respectively.

Proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by US FDA-defined snapshot algorithm will be analyzed similarly to the primary efficacy endpoint. However, the noninferiority margin used for the proportion of subjects with HIV-1 RNA < 50 copies/mL will be 10%.

Similarly to the primary efficacy endpoint, noninferiority will be assessed using the conventional CI approach. The point estimate of treatment difference (B/F/TAF group – DTG+F/TAF group) in the percentage of subjects with HIV-1 RNA < 50 copies/mL and the associated 2-sided 95.001% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

It will be concluded that B/F/TAF is noninferior to DTG+F/TAF if the lower bound of the 2-sided 95.001% CI of the difference between treatment groups (B/F/TAF group – DTG+F/TAF group) in the percentage of subjects with HIV-1 RNA < 50 copies/mL is greater than −10%.

The above analysis will be performed using both the FAS and the Week 48 PP analysis set.

In addition, the following analyses will be performed using the FAS to evaluate the interaction between region and treatment to assess homogeneity of treatment effect across different regions.

A region is defined as multiple sites combined based on geographical locations (see Appendix 2 for region definition).

For each region, the difference in the proportion of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI will be calculated based on an unconditional exact method using 2 inverted 1-sided tests.

The CMH analysis will be used to estimate the odds ratio and corresponding 95% CI for each region and overall. The homogeneity of the odds ratios across different regions will be tested using a Breslow-Day test and a corresponding p value will be reported.

6.1.2.2.2. Subgroup Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 48 as Determined by US FDA-defined Snapshot Algorithm

Since the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm (primary endpoint) is expected to be very low (around 2%), the efficacy analysis by subgroup will be conducted by assessing the proportion of subjects with HIV-1 RNA < 50 copies/mL determined by the US FDA-defined snapshot algorithm at Week 48 (a secondary efficacy endpoint) within each subgroup specified in Section 3.4.1 based on the FAS for randomized phase analysis.

For each level of subgroup factors, the proportion difference between treatment groups and the associated 2-sided 95% CIs will be computed based on an unconditional exact method using 2 inverted 1-sided tests.

Additionally, a logistic regression model will be performed which include subgroup, treatment, and treatment by subgroup interaction. The odds ratio and the associated 95% CI will be estimated within each subgroup. The homogeneity of the treatment effects between subgroups will be evaluated using a Wald test based on the interaction between treatment and the subgroup factor.

A forest plot of the treatment differences in HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) at Week 48 and their associated 95% CIs for each subgroup will be generated.

6.1.2.2.3 Analysis of CD4+ Cell Count

All CD4+ cell count will be summarized by visit using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of blinded study drug) for subjects in the FAS for randomized phase analysis and for subjects in all B/F/TAF Analysis Set for all B/F/TAF analysis.

The changes from baseline in CD4+ cell count at Week 48 will be summarized by treatment group using descriptive statistics for randomized phase analysis. The differences in changes from baseline in CD4+ cell count between the 2 treatment groups and the associated 95% CI will be constructed using analysis of variance (ANOVA) models, including treatment group as a fixed effect in the model. The change from baseline in CD4+ cell count will also be summarized at visits other than Week 48 by treatment group for the FAS for randomized phase analysis.

The change from baseline in CD4+ cell counts will also be analyzed based on the Week 48 PP analysis set for randomized phase analysis.

The mean and 95% CI of change from baseline in CD4+ cell count over time will be plotted for the FAS for randomized phase analysis.

In addition, the change from baseline in CD4+ cell counts with missing values imputed using the last observation carried forward (LOCF) method will be summarized at each visit (up to week 48 visit) based on the FAS for randomized phase analysis. 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, data collected up to 1 day after permanent discontinuation of study drug) observed before the analysis visit window that has the missing value.
- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no non-missing postbaseline observation collected prior to that visit.

The changes from baseline in CD4+ cell count will be summarized by treatment group and scheduled visits using descriptive for all B/F/TAF analysis.

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.2. Efficacy Analysis for All B/F/TAF Analysis

6.2.1. Definition of the Efficacy Endpoint

The efficacy endpoints for all B/F/TAF analysis include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL by M = E approach
- The change from baseline in CD4+ Cell Count and CD4 percentage (%) by visit

The analyses for the efficacy endpoints above will be conducted using the All B/F/TAF Analysis Set.

6.2.2. Analysis of the Efficacy Endpoints for All B/F/TAF Analysis

6.2.2.1. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL by Missing = Excluded Approach

The proportion of subjects with HIV-1 RNA < 50 copies/mL will be analyzed using M = E for imputing missing HIV-1 RNA values using the All B/F/TAF Analysis Set for the all B/F/TAF analysis.

- 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 All B/F/TAF Analysis Set with non-missing HIV-1 RNA value at that visit.

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

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL

The 95% CI for the proportion of subjects with HIV-1 RNA < 50 copies/mL for a treatment group will be constructed using the Clopper-Pearson exact method. No statistical comparisons will be made for the all B/F/TAF analysis.

6.2.2.2. Analysis of CD4+ Cell Count and CD4%

The analysis of CD4 cell count will be based on on-treatment data (ie, up to 1 day after the last dose date of study drug) using the All B/F/TAF Analysis Set for the all B/F/TAF analysis.

The changes from baseline in CD4+ cell count at each visit will be summarized by treatment group using descriptive statistics. No statistical comparisons will be made for the all B/F/TAF analysis.

Similar analysis will be conducted for CD4% using the All B/F/TAF Analysis Set for the all B/F/TAF analysis.

In addition, the mean and 95% CI of change from baseline in CD4+ cell count over time will be plotted for the all B/F/TAF analysis.

6.3. Changes From Protocol-Specified Efficacy Analyses

No change from the protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

Safety data will be summarized by treatment group for the subjects in the Safety Analysis Set for the randomized phase analysis, and the subjects in the All B/F/TAF Analysis Set for the all B/F/TAF analysis, unless specified otherwise. All safety data from both phases of the study will be included in data listings.

For the randomized phase analysis, the terms "study drug start date (ie, the first dose date)", "study drug stop date (ie, the last dose date)", and "baseline" in the text below refer to the first dose date, the last dose date, and baseline defined for the randomized phase analysis; the term "study drug" in the text below refer to the randomized study drugs.

For the all B/F/TAF analysis, the terms "study drug start date (ie, the first dose date)", "study drug stop date (ie, the last dose date)", and "baseline" in the text below refer to the first dose date, the last dose date, and baseline defined for the all B/F/TAF analysis; the term "study drug" in the text below refer to B/F/TAF.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions 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 Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug, or
- Any AEs leading to premature discontinuation of study drug.

  More specifically, the AE onset date will be compared with the first and last randomized study drug dates for the randomized phase analysis. For the all B/F/TAF analysis, the AE onset date will be compared with the first and last study drug dates.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if 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 dosing date of 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 the last dose of study drug

An AE with completely missing onset date and stop date or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of study drug, will be considered to be treatment emergent. 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 dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Death

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group. All AEs summary will use both the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively.

- Any Grade 2, 3, or 4 treatment-emergent AEs
- Any Grade 3 or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs

- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- 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 treatment group and by the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last 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 alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all treatment-emergent AEs, Grade 3 or 4 treatment-emergent AEs, treatment-emergent study drug-related AEs, Grade 2, 3, or 4 treatment-emergent study drug-related AEs, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency.

Summary of treatment-emergent AEs by SOC and PT will also be conducted for all subgroups listed in Section 3.4.2 for randomized phase analysis.

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

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study-Drug-Related SAEs
- Deaths report
- AEs leading to premature discontinuation of study drug

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. 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 diagnoses (see Appendix 6 of the protocol). 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 illness definition of an AIDS-Defining Diagnosis will be listed.

7.1.7.2. Cardiovascular or Cerebrovascular Events

Preferred terms for cardiovascular or cerebrovascular events are from relevant Standardized MedDRA Query (SMQ). The selected PT listing was provided by GLPS and reviewed by Gilead medical monitors (see details in Appendix 5).

The number and percentage of subjects with treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be summarized by treatment group based on the safety analysis set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using the Fisher's exact test for randomized phase analysis. No statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed for all B/F/TAF analysis. A data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. 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 GLPS and reviewed by Gilead medical monitors (see details in Appendix 6).

The number and percentage of subjects with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group based on the safety analysis set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using the Fisher's exact test for randomized phase analysis. No statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed for all B/F/TAF analysis. A data listing of hepatic events will be provided.

7.1.7.4. COVID-19

A data listing of TEAEs for COVID-19 and Suspected COVID-19 infection (see definition in Appendix 4) will be provided.

7.2. Laboratory Evaluations

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

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

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group based on the safety analysis set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis for each laboratory test specified in the study protocol as follows:

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

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

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

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn 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 (years)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms, and SCr is serum creatinine.

7.2.2. Graded Laboratory Values

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

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of 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 results 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 (including glucose results without a known fasting status) will be summarized, as nonfasting glucose was not assessed at baseline visit for most of the subjects; therefore, an abnormality is treatment-emergent or not cannot be determined for these subjects.

Both urine red blood cell (RBC) based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed and assigned a toxicity grade in this study. Hematuria (Quantitative) is a reflex test. Urine RBC based on microscopic examination or dipstick will be presented in laboratory toxicity summary tables and listings.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by laboratory test and treatment group based on Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively; subjects will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent Grade 2, 3 and 4 laboratory abnormalities

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

A by-subject listing of all treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.2.3. 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 based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be estimated from a 2-sided Wilcoxon rank sum test for randomized phase analysis. No formal statistical testing is planned for all B/F/TAF analysis.

For randomized phase analysis, the number and percentage of subjects who took lipid modifying medications at study entry and initiated the medications during the randomized phase of study will be provided by treatment group based on the Safety Analysis Set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test. For all B/F/TAF analysis, the number and percentage of subjects who took lipid modifying medications at the First Dose of B/F/TAF and While Receiving B/F/TAF will be provided by treatment group based on the All B/F/TAF Analysis Set. No formal statistical testing is planned for all B/F/TAF analysis.

A lipid modifying medication is defined as a medication with drug class (based on the World Health Organization [WHO] Drug ATC2 term) = "LIPID MODIFYING AGENTS" and WHO Drug preferred drug name containing the wording of "STATIN".

For randomized phase analysis, a sensitivity analysis of fasting lipid tests will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications during the study: baseline values, Week 48 values, and changes from baseline at Week 48 will be summarized by treatment group using descriptive statistics for randomized phase analysis. Baseline and change from baseline at Week 48 will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test for randomized phase analysis. Only subjects with both baseline and Week 48 postbaseline values will be included in the analysis.

Summary of baseline, postbaseline, and change from baseline in fasting metabolic laboratory tests will be repeated within each subgroup of baseline NRTI backbone (F/TAF vs. F/TDF) based on the Non-Study ARV Medication eCRF based on the Safety Analysis Set for randomized phase analysis. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be generated from a 2-sided Wilcoxon rank sum test for randomized phase analysis.

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted by treatment group based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively.

7.2.4. 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 based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively:

- Aspartate aminotransferase (AST): (a) > 3 × Upper limit of normal (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 summary will include data from all postbaseline visits up to 30 days after the last dose of 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. For randomized phase analysis, the denominator is the number of subjects in the safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date. For all B/F/TAF analysis, the denominator is the number of subjects in the ALL B/F/TAF analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

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

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group and visit using descriptive statistics based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test for randomized phase analysis. No formal statistical testing is planned for all B/F/TAF analysis.

In addition, ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare, defined as ALT elevations confirmed at two consecutive visits, will be evaluated and listed for subjects with HIV/HBV coinfection at baseline for randomized phase analysis and B/F/TAF phase analysis. The first occurrence of two or more consecutive ALT elevations will be identified as the ALT flare.

7.2.5. Renal-Related Laboratory Evaluations

7.2.5.1. Serum Creatinine and $eGFR_{CG}$

Baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be summarized by treatment group and visit using descriptive statistics based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test for randomized phase analysis. No formal statistical testing is planned for all B/F/TAF analysis.

Median (Q1, Q3) of change from baseline in serum creatinine and $eGFR_{CG}$ over time will be plotted by treatment group based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively.

Summary of baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be repeated within each subgroup of baseline NRTI backbone based on the Non-Study ARV Medication eCRF (F/TAF vs. F/TDF) based on the Safety Analysis Set for randomized phase analysis. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be generated from a 2-sided Wilcoxon rank sum test for randomized phase analysis.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group for vital signs and body weight as follows based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

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

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

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

7.4. Prior and Concomitant Medications

7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications used prior to, during, or after the study (if collected) will be coded using the Gilead-modified WHO Drug Dictionary for ARV medications. The WHO preferred drug 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.

7.4.2. 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 Drug preferred drug name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 up to the last dose date will be summarized (number and percentage of subjects) by treatment group and preferred drug name based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Multiple drug use will be counted only once per subject for each preferred drug name. The summary will be sorted by decreasing total frequency. For drugs with the same frequency, sorting will be done alphabetically.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) 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 non-ARV medications are complete, the start date is not after last dose date and the stop date is not before first dose date, or the non-ARV medications are marked as ongoing and start date is on or before last dose date, the non-ARV medications are concomitant. For the randomized phase analysis, Study Day 1, the first and last dose dates refer to Study

Day 1, the first dose date and the last dose date defined for the randomized phase analysis. For the all B/F/TAF analysis, Study Day 1, the first and last dose dates refer to Study Day 1, the first dose date and the last dose date defined for the All B/F/TAF analysis.

Summaries of non-ARV concomitant medications will be provided based on the Safety Analysis Set for randomized phase analysis and All B/F/TAF Analysis Set for all B/F/TAF analysis, respectively. Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

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

7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study. Physical examination data was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the safety analysis set for randomized phase analysis.

7.8. Changes From Protocol-Specified Safety Analyses

No change from the protocol-specified safety analysis is planned.

8. SPECIAL POPULATION ANALYSES

Special population analyses will be performed by treatment group based on the Safety Analysis Set for randomized phase analysis and all B/F/TAF analyses (if applicable). Study Day 1, the first and last dose dates refer to Study Day 1, the first dose date and the last dose date defined for the randomized phase analysis and all B/F/TAF analyses (if applicable).

8.1. Analyses for HIV/HBV Coinfected Subjects

Subjects with HIV/HBV coinfection at baseline for randomized phase analysis and for all B/F/TAF analyses are defined as subjects meet any of the following two criteria for each analysis:

- Positive HBsAg on or prior to the first dose date, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.

The following summary analyses will be conducted by treatment group and overall for subjects with HIV/HBV coinfection at baseline for randomized phase analysis and for all B/F/TAF analyses:

- The proportion of subjects with HBV DNA < 29 IU/mL at baseline and Week 48 by missing = excluded approach.
- The change from baseline in $\log_{10}$ HBV DNA ($\log_{10}$ IU/mL)
- Treatment-emergent adverse events overall summary
- Treatment-emergent adverse events by SOC, HLT, and PT
- Treatment-emergent laboratory abnormalities
- The change from baseline for liver-related laboratory tests, including ALT, AST, ALP, total bilirubin, direct and indirect bilirubin.

For summary, HBV DNA will be analyzed for all visits using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug) for subjects with HIV/HBV coinfection at baseline for randomized phase analysis using FAS and for all B/F/TAF analyses using all B/F/TAF set.

The following listings will be provided for subjects with HIV/HBV coinfection at baseline for safety analysis set and for all B/F/TAF analysis set.

- Listing of adverse events
- Listing of liver-related laboratory tests and HBV DNA results
- Listing of ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare (see Section 7.2.4)

Subjects with incident HIV/HBV coinfection while on study drug for randomized phase analysis and for all B/F/TAF analyses are defined as subjects who are not HIV/HBV coinfected at baseline and meet any of the following criteria for each analysis:

- Positive HBsAg after the first dose date and on or prior to the date of permanent discontinuation of study drug, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) after the first dose date and on or prior to the date of permanent discontinuation of study drug, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") after the first dose date and on or prior to the date of permanent discontinuation of study drug: Acute hepatitis B, Chronic hepatitis B, Congenital hepatitis B infection, Hepatitis B, Hepatitis B core antibody positive, Hepatitis B DNA assay positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive.

The following listings will be provided for subjects with incident HIV/HBV coinfection while on study drug (if any) for safety analysis set and for all B/F/TAF analysis set.

- Listing of adverse events
- Listing of liver-related laboratory tests and HBV DNA results

8.2. Analyses for HIV/HCV Coinfected Subjects

Subjects with HIV/HCV coinfection at baseline are defined as subjects with positive HCVAb and quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date. The following analyses will be provided for subjects with HIV/HCV coinfection at baseline for randomized phase analysis and for all B/F/TAF analysis:

- Listing of adverse events
- Listing of liver-related laboratory tests and HCV RNA results

Subjects with incident HIV/HCV coinfection while on study drug are defined as subjects who are not HIV/HCV coinfected at baseline and meet any of the following criteria:

- Positive HCVAb after the first dose date and on or prior to the date of permanent discontinuation of study drug with baseline HCVAb Negative or missing, or
- Quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) after the first dose date and on or prior to the date of permanent discontinuation of study drug, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") after the first dose date for randomized phase analysis and on or prior to the date of permanent discontinuation of study drug: Acute hepatitis C, Chronic hepatitis C, Hepatitis C, Hepatitis C antibody positive, Hepatitis C RNA positive, Hepatitis C virus test positive.

The following listings will be provided for subjects with incident HIV/HCV coinfection while on study drug for randomized phase analysis and for all B/F/TAF analysis:

- Listing of adverse events
- Listing of liver-related laboratory tests and HCV RNA results

9. REFERENCES

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

10. SOFTWARE

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

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

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for actual sample size and power calculation.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

Study Procedures	Screening[a]	Day 1	Week[b,c] 4	8	12	24	36	48	Post-Week 48 Every 12 Weeks[c,d]	End of Blinded Treatment Visit[e]	Open Label Extension (OL) Weeks[c,f] 12 OL	24 OL	36 OL	48 OL	60 OL	72 OL	84 OL	96 OL	30 Day Follow up[g]	ESDD[h]
Informed Consent	X																			
Questionnaires[i]		X	X		X			X												
Medical History	X																			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]
Complete/ Symptom-Directed[k] Physical Exam	X	X	X	X	X	X	X	X	X[l]	X	X	X	X	X	X	X	X	X	X[j]	X[j]
12-Lead ECG (performed supine)	X																			
Height	X																			
Vital signs[m] and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]
Serum Pregnancy Test[n]	X																			
Urine Pregnancy Test[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
Chemistry Profile[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j,o]
eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X
Hematology Profile[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]
Metabolic Assessments[q]		X			X	X		X	X[r]	X		X		X		X		X		
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				

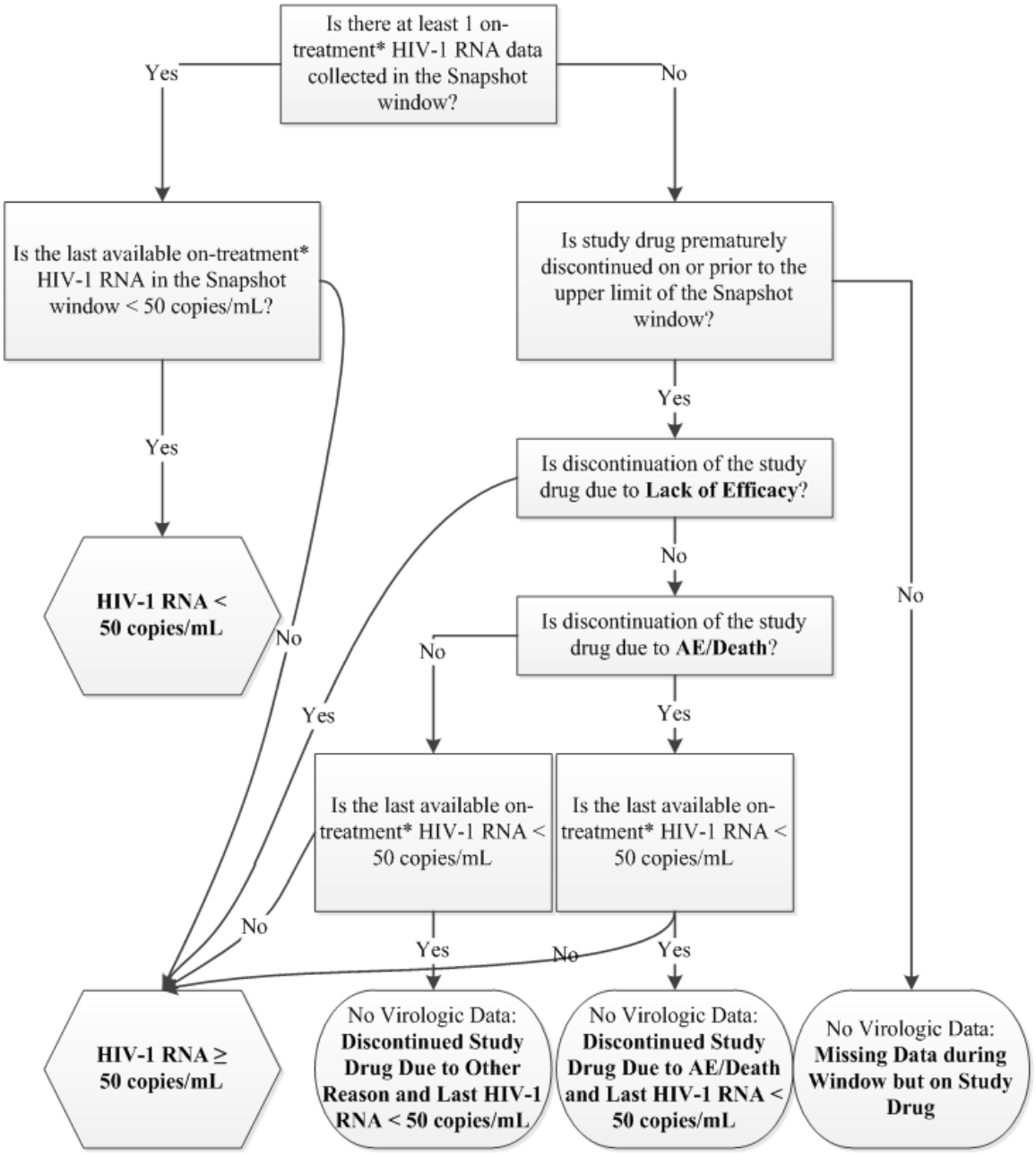
Study Procedures	Screening[a]	Day 1	Week[b,c] 4	8	12	24	36	48	Post-Week 48 Every 12 Weeks[c,d]	End of Blinded Treatment Visit[e]	Open Label Extension (OL) Weeks[c,f] 12 OL	24 OL	36 OL	48 OL	60 OL	72 OL	84 OL	96 OL	30 Day Follow up[g]	ESDD[h]
CCI																				
CD4+ Cell Count and Percentage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Serology[s]	X							X	X[l]					X				X		
HBV blood panel[t]	X[u]							X[u]	X[u]					X[u]				X[u]		
Plasma HBV DNA[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization[w]		X																		
Study Drug Dispensation		X[x]	X	X	X	X	X	X	X	X[y]	X	X	X	X	X	X	X			
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
HIV-1 Genotype/ Phenotype[c]																				X[c]
CCI																				

a. Evaluations to be completed within 30 days prior to Day 1.
b. Study visits are to be completed within ± 2 days of the protocol specified visit date (based on the Day 1) through Week 12 and within ± 6 days through to Week 36, unless otherwise specified. The visit window for Week 48 will be ± 6 weeks of the protocol specified visit date.
c. HIV-1 genotype and phenotype testing for subjects with confirmed virologic failure and HIV-1 RNA >200 copies/mL. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV-1 RNA and HIV-1 resistance analysis (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Protocol Section 6.11).
d. After Week 48, all subjects will continue to take their blinded study drug and attend visits every 12 weeks (± 6 days of the protocol specified visit date) until the End of Blinded Treatment Visit.
e. Once the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF is demonstrated following review of unblinded data, subjects in a country where B/F/TAF FDC is not available, will be given the option to receive B/F/TAF FDC in an OL extension phase for up to 96 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in that country, whichever occurs first. Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.
f. Study visits are to be completed within ± 6 days of the protocol specified visit date based on the End of Blinded Treatment Visit date, unless otherwise specified.

g. **Before the OL extension period**, 30-Day Follow-up is required for subjects not enrolling in the OL extension, or those who prematurely discontinue study drugs and do not continue in the study through at least one subsequent visit after the Early Study Drugs Discontinuation Visit.
During the OL extension period, subjects who complete the OL extension, or who permanently discontinue study drugs during the OL extension, will be required to return to the clinic 30 days after the last dose of study drugs, for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
h. **Before the OL extension period**, Early Study Drugs Discontinuation visit is to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit, even if the subject discontinues study drugs.
During the OL extension period, subjects who discontinue study drug will be asked to return to the clinic within 72 hours of stopping study drugs, for the Early Study Drugs Discontinuation Visit, followed by a 30-Day Follow-Up Visit. The subject will not continue attending the scheduled OL study visits.
i. SF-36, HIV Symptoms Distress Module, WPAI, PSQI, to be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
j. Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.
k. Symptom-directed physical examination, as needed.
l. Post Week 48, complete physical examination and HCV Serology, are to be performed every 48 weeks
m. Blood pressure, pulse, respiration rate, and temperature.
n. Females of childbearing potential only. After the Screening visit, positive urine pregnancy tests will be confirmed with a serum pregnancy test.
o. Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). After Day 1, calcium, phosphorous, and magnesium will not be collected. Analyses of glucose will be done as part of the fasting metabolic assessments, and not as part of the chemistry profile at Day 1, Weeks 12, 24, 48, post Week 48 (every 24 weeks), and End of Blinded Treatment, Week 24OL, Week 48OL, Week 72OL, Week 96OL.
p. CBC with differential and platelet count.
q. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) 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.
r. Metabolic assessments during the post Week 48 will be done every 24 weeks.
s. Hepatitis C virus serology. Subjects who are HCVAb positive will have a HCV RNA test performed.
t. HBV blood panel will be performed at **Screening, Week 48, every 48 weeks through End of Blinded Treatment Visit, and Weeks 48OL, 96OL**: HBsAg, HBsAb, HBcAb
u. **For subjects who are HBV co-infected at any visit:** The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative), and HBeAg (if negative, reflex HBeAb)
For subjects who are NOT HBV co-infected at any visit: The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBcAb, and HBsAg. Subjects who are HBsAg or HBcAb positive will have a reflex test for HBV DNA (viral load)
v. **For subjects who are HBV co-infected at any visit:** Plasma HBV DNA at every visit (including OL extension period [not collected at Screening and 30-day Follow-up])
w. Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.
x. Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit.
y. Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the OL extension for up to 96 weeks.
cc [redacted]

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Switch Trial)

The following flowchart for US FDA-defined snapshot algorithm is 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 HIV-1 RNA data include all HIV-1 RNA data for subjects who are on-going and HIV-1 RNA data up to 1 day after the last dose date of study drug for subjects who prematurely discontinue or complete study drug.

Appendix 3. Region Definition

Region	Country Name	State	No. of Subjects in Safety Analysis Set or FAS (N=565)	Total No. of Subjects by Region in Safety Analysis Set or FAS Set (N=565)
Region 1	CANADA (CAN)		49	49
Region 2	AUSTRIA (AUT)		3	85
	FRANCE (FRA)		26	
	GERMANY (DEU)		56	
Region 3	United States (USA)	CA	63	83
	United States	HI	4	
	United States	WA	16	
Region 4	United States	AZ	3	64
	United States	CO	2	
	United States	NM	6	
	United States	TX	53	
Region 5	United States	KY	6	33
	United States	MI	3	
	United States	MN	12	
	United States	MO	12	
Region 6	United States	DC	28	82
	United States	MA	35	
	United States	NJ	4	
	United States	NY	15	
Region 7	United States	GA	31	67
	United States	LA	0	
	United States	NC	33	
	United States	SC	3	
Region 8	United States	FL	70	102
	United States	PR*	32	

* PR = Puerto Rico.
Note: In general, a region is defined as multiple sites combined based on geographical locations. For example, for international studies, sites from each country or multiple neighboring counties were combined; and for US studies, sites from each state or multiple neighboring states were combined.

Appendix 4. COVID-19 related Adverse Events

An adverse event record will be flagged as a COVID-19 related adverse event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following SMQs under MedDRA v23.1 provided by Gilead GLPS (search name: COVID-19 (SMQ) – Narrow) and reviewed by Gilead medical monitors.

	SMQ Source
COVID-19 related Events	**COVID-19 (SMQ) (Narrow Scope)**

Appendix 5. 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 v23.1 provided by Gilead GLPS (search name: Essential ischaemic cardiac and cerebral events without supportive tests and conditions) and reviewed by Gilead medical monitors and GLPS safety physician.

	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 6. 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 v23.1 provided by Gilead GLPS (search name: Non-infectious, non-congenital hepatobiliary disorders in Final_MST_Global_v23.1_05Nov2020) and reviewed by Gilead medical monitors and GLPS safety physician.

	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 7. Determining Missing and Virtual Visits Due to COVID-19

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

Data collection

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

Determination of Missed and Virtual visits

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

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

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

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

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

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

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

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

iii. Otherwise result is missing

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

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

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

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

Appendix 8. Programming Specification

1) AGE calculated as follows

   a) AGE (years) is calculated from the number of days between the date of birth (DOB) and Day 1 (first dose date) defined for both randomized phase analysis and all B/F/TAF analysis. For subjects randomized to DTG + F/TAF group, AGE (years) is calculated for both randomized phase analysis and all B/F/TAF analysis.

   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 randomized and never dosed with study drug, age will be calculated from the date of randomization.

   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 (ie, with non-missing screening date) and have a screening number. For summaries the same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used to identify 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 randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) are derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if subject never dosed.

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

7) Body mass index (BMI) and Body Surface Area (BSA)

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

   - BMI = (weight [kg]) / (height [meters]^2)
   - BSA (m^2) = SQRT([Height(cm) × Weight(kg)] / 3600)

   Baseline height and weight will be used for this calculation.

8) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

   a) CMH test for nominal variable (Y), the p-value from general association test should be used for nominal variable:

```
proc freq order=adsl;
   tables trtgrp * Y /cmh /*general association test*/
run;
```

   b) CMH test for ordinal variable (Y), the p-value from row mean score test should be used for ordinal variable:

```
proc freq order=adsl;
   tables trtgrp * Y / cmh2 ; /*row mean score test*/
run;
```

   c) Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variable:

```
proc npar1way wilcoxon data=adsl;
   class trtgrp;
   var Y;
run;
```

9) Please note, “Not Permitted”, “Unknown”, or missing categories will be excluded percentage calculation and also excluded for p value generation for categorical data analysis (eg, CMH test or Fisher exact test). 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% and no p-value will be generated.

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

10) SAS code for treatment comparison for duration of exposure. The p-value from log rank test should be used.

```
proc lifetest data=ADSL method=km;
    time TRTDURD*ESDD(0); /*Derive ESDD from COMT01FL, where ESDD = 0
    indicates censored observation (ie, subjects completed study drug)*/
    Strata TRT01AN;
    label TRTDURD = "Duration of Exposure (Days)";
run;
```

11) Last Dose Date and Last Study Date

a) Last Dose Date (ie, TRTEDTC, TRTEDT, TR01EDT or TR01EDTC) in ADSL for randomized phase analysis and all B/F/TAF analysis was defined in SAP Section 3.8.1.

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

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

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.

12) Duration of baseline ARV regimen

a) Defining ARV Regimen at Baseline:

All subjects are expected to enter the study on DTG + F/TAF or DTG + F/TDF. Using the ARV raw dataset, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT ='Prior ARV" or "Current ARV"), taken on or up to 2 day prior to first dose date (or randomization date if not treated) for randomized phase analysis:

Select only ARV with the start date on or prior to first dose date of randomized study drug, and the end date ongoing or >= the first dosed date of randomized study drug, (For the same ARV, if the stop date of 1 record is on the same date or 1 day before the start date of another record, please combine it as one record)

When determining the baseline ARV regimen, look at the ingredient of drugs, replacing "_" with "/" (for FTC_TAF and FTC_TDF), respectively. Moreover, replace "FTC/" with "F/". Assign an order priority of 1 to "DTG" and 2 to "F/TAF" or "F/TDF" for each subject.

Once the ingredients have been updated and assigned an appropriate priority, transpose the ingredients by subject (using the ingredient as the variable and priority as the id) and concatenate each column with a "+" following the priority specified above. To illustrate this, if a subject is on DTG and FTC_TAF, then their regimen would be presented as "DTG+F/TAF".

b) Calculation of the duration of baseline ARV regimen

Duration of baseline regimen DTG + FTC/TAF or DTG + FTC/TDF prior to the randomized phase 1st dose date (or B/F/TAF first dose date) is defined as (End Date – Start Date+1) (ie, equal to [randomized first dose date (or B/F/TAF first dose date)-1 – start date of prior ARV +1)]. Duration will be expressed in years so that duration in days will be divided by 365.25 days.

End date is defined as randomized phase first dose date (or B/F/TAF first dose date) -1 or randomized date if randomized but not dosed,

Start Date: The use of baseline ARV regimen: DTG + DESCOVY (FTC/TAF) or DTG + TRUVADA

Step 1: Use the following rules to handle any incomplete start dates

- If only month and year are available, day will be first imputed as 15th, then imputed as minimum of (the start date of the ARV, randomized phase 1st dose date-1, the stop date of the same ARV)
- If only year is available, month and day will be first imputed July 1st of the year, then imputed as minimum of (the start date of the ARV, randomized phase 1st dose date-1, the stop date of the same ARV)
- No imputation applied for date missing completely

(Use the following rules to handle any incomplete stop dates, if needed

- If only month and year are available, day will be first imputed as 15th, then imputed as minimum of (the randomized phase 1st dose date-1, the stop date of the same ARV)
- If only year is available, month and day will be first imputed July 1st of the year, then imputed as minimum of (randomized phase 1st dose date-1, the stop date of the same ARV)
- No imputation applied for date missing completely)

Step 2: Select ARVs with start date on or prior to the randomized phase 1st dose date (or B/F/TAF first dose date for all B/F/TAF analysis)

Step 3: For each subject, find the first dose date and last dose date for each study drug component:

For the same ARV, if the stop date of 1 record is on the same date or 1 day before the start date of another record, please combine it as one record.

- Select all ARVs containing the wording of 'DTG' in ARV.INGRED and select the latest start date (D1_DTG)

- Select all ARVs containing the wording of 'FTC_TAF' in ARV.INGRED and select the latest start date (D1_DESCOVY)
- Select all ARVs containing the wording of 'FTC_TDF' in ARV.INGRED and select the latest start date (D1_TRUVADA)

Step 4: Determine of the start date of ARV regimen

- The start date of DTG+DESCOVY (D1_DTG+DESCOVY) after taking into account all 2 components of DTG, DESCOVY is the latest start date of D1_DTG, D1_DESCOVY
- The start date of DTG+ TRUVADA (D1_DTG+TRUVADA)after taking into account all 2 components of DTG, DESCOVY is the latest start date of D1_DTG, D1_TRUVADA

13) Toxicity Grades:

a) For toxicity grade summaries, include all post-baseline graded results up to 30 days after the last dose of study drug, not just those used in by-visit summaries.

b) For glucose grading, as specified in SAP Section 7.2.2.1, the treatment-emergent flag cannot be determined for nonfasting glucose (including glucose results without a known fasting status). As a result, these records will be excluded from the "Maximum Treatment-emergent Toxicity Grade" summary in the "Treatment-emergent Laboratory Abnormalities" or "Treatment-emergent Grade 3 or 4 Laboratory Abnormalities" summary tables. In addition, fasting glucose and non-fasting glucose will be listed as two separate laboratory tests in the "Laboratory Abnormalities" and "Grade 3 or 4 Laboratory Abnormalities" listings. Only a maximum postbaseline toxicity flag will be displayed and the treatment-emergent flag will not be displayed for nonfasting glucose as the treatment-emergent flag cannot be determined for nonfasting glucose.

14) Efficacy analyses:

a) For categorical efficacy response (eg, Subjects with HIV-1 RNA < 50 copies/mL or Subjects with HIV-1 RNA ≥ 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between two treatment groups and its 95.002% CIs (for HIV-1 RNA < 50 at wk48 by snapshot algorithm for FAS or Week 48 PP set) or 95% CIs are calculated based on the an unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

b) The following SAS code will be used to compute difference in percentage, its 95.001%CI and p-value.

```
data example;
input  grp trt01a $  outcome $ count ;

datalines;
1       Treat-A        2-Fail        1
1       Treat-A        1-Succ      189
1       Treat-B        2-Fail        4
```

```
1       Treat-B        1-Succ       88
run;

proc freq data = example;
table trt01a*outcome /riskdiff(CL=(exact)) alpha=0.04999;
weight count; exact RISKDIFF(METHOD=SCORE);
output out=ciexact(keep=_RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;

c
data final(keep=A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate ="Percentage Difference"
LowerCL = "95% Lower Confidence Limit"
UpperCL = "95% Upper Confidence Limit"
A1 = "Percentage of Success in Treat-A"
B1 = "Percentage of Success in Treat-B";
Estimate=100*_RDIF1_;
LowerCL = 100*XL_RDIF1;
UpperCL = 100*XU_RDIF1;
A1 = 100*_RSK11_;
B1 = 100*_RSK21_;
ocharc1 = right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

c) Please note, alpha=0.04999 is only used for the primary efficacy endpoint (HIV-1 RNA >= 50 c/mL by snapshot algorithm at Week 48) to obtain 95.001% CIs and the endpoint of subjects with HIV-1 RNA < 50 c/mL by snapshot algorithm at Week 48 in FAS and Week48 PP analysis set; otherwise, for the efficacy endpoints with proportions, the alpha=0.05 is used to obtain 95% CIs.

d) The 95% CI for percentage estimate of HIV-1 RNA < 50 copies/mL for each treatment is calculated based on the Clopper-Pearson exact method.

e) Fisher's exact test for categorical efficacy response (eg, HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm), where *trtgrp* is the treatment, and *response* is the categorical efficacy response. P-value from 2-sided Fisher's exact test should be used to test superiority.

```
proc freq data=adeff;
   tables trtgrp*response/fisher; /*p value from Fisher's exact test*/
run;
```

f) Homogeneity test: Homogeneity Test of Treatment Effect (HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm) Across Region in HIV-1 RNA < 50 copies/mL at Week 48 (Snapshot Algorithm). For each region, the odds ratio and its 95% CI are calculated from the CMH test. For overall, the odds ratio and its 95% CI are calculated based on the common odds ratio estimate from the CMH test. The p-value for the homogeneity test is based on the Breslow-Day test of the interaction between region and treatment group as follows.

```
proc freq data=xxx;
   tables region*trtgrp* response /all; /*p value from Breslow Day test,
   (trtgrp: 1, 2; response: 1: < 50, 2: >=50)*/
run;
```

g) Subgroup analyses for HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm

For the subgroups of age, sex, race, baseline CD4 cell count, and study drug adherence, the proportion difference between two treatment groups and its 95% CIs are calculated based on an unconditional exact method using 2 inverted 1-sided tests, similarly to that for the primary efficacy endpoint.

h) Homogeneity test: Homogeneity Test of Treatment Effect (HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm) between Subgroups in HIV-1 RNA < 50 copies/mL at Week 48 (Snapshot Algorithm)

a. For the subgroups of age, sex, race, region and study drug adherence, the odds ratio and the associated 95% CIs are estimated for the response variable (response; coded as 1 for success and 0 for non-success) using a logistic regression model including subgroup factor (coded as 1 for the first subgroup and 2 for the second subgroup), treatment (trtgrp; coded as 1 for active [ie, B/F/TAF] and 2 for control), and treatment by subgroup factor.

eg. region stratum (region; coded as 1 for “US” and 2 for “Ex-US”)

For example, for the age subgroup (agegrp; coded as 1 for < 50 and 2 for >= 50), the following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup:

Note: For the following code, it is assumed that none of the variables have any formats applied to them. If they do, they must be removed before calling the code.

e.g. for the age subgroup, the following codes will be used to get Odds Ratio and 95% CI within subgroup:

```
proc genmod data=data descending;     /*model for success*/
    class trtgrpn agegrp;
    model response = trtgrpn agegrp trtgrpn*agegrp/dist=bin
    link=logit lrci;
    estimate 'Group 1' trtgrpn 1 -1 trtgrpn*agegrp 1 0 -1 0/exp;
    estimate 'Group 2' trtgrpn 1 -1 trtgrpn*agegrp 0 1 0 -1/exp;
run;
```

Note: trtgrpn is the numeric treatment group variable, response is the response outcome variable (1 vs 0 (’<50’ vs’>=50’)), agegrp is the subgroup variable for age (1:< 50 vs 2: >= 50).

(P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup. Odds ratio is from L'Beta estimate, its 95%CI is from L'Beta confidence limits for each subgroup.)

i) ANOVA model for continuous efficacy variable (eg, CD4): The differences in changes from baseline in CD4 cell count between treatment groups and the associated 95% CI will be constructed using an ANOVA, including treatment as fixed effect in the model.

```
proc glm data=adeff;
      class trtgrp;
      model CD4=trtgrp;
      lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

j) Listing for US FDA-defined snapshot outcome:

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

i) HIV-1 RNA >= 50 copies/mL - Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA >= 50 copies/mL

ii) HIV-1 RNA >= 50 copies/mL - Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA >= 50 copies/mL

iii) No virologic Data – Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL

iv) No virologic Data – Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA < 50 copies/mL

Note: * 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.

15) Clarification of the following LOCF algorithms:

- Baseline values will 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) TEAE

Events with Missing Onset Day and/or Month

An event is treatment emergent if the following 3 criteria are met:

1) 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 study drug, and

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

3) End date is as follows:

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

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

   c) End date is completely missing

Events with Completely Missing Onset Date

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

17) 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)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

* Due to the reflexive nature of the quantitative urine RBC test, results will be combined with the dipstick test of urine blood as described below:

Is Post-BL Urine RBC (Quant.) Result Available?	Is BL Urine RBC (Quant.) Result Available?	Is Post-BL Urine Blood (Dipstick) Result Available?	Is BL Urine Blood (Dipstick) Result Available?	How to Determine Treatment-Emergent Toxicity for "Urine RBC (Hematuria, Quantitative or Dipstick)"
Yes	Yes	-	-	Compare post-BL Urine RBC (Quant.) toxicity grade to BL Urine RBC (Quant.) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
Yes	No	-	-	Treatment-emergent. Use post-BL Urine RBC (Quant.) toxicity grade.
No	-	Yes	Yes	Compare post-BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
No	-	Yes	No	Treatment-emergent. Use post-BL Urine Blood (Dipstick) toxicity grade.
No	-	No	-	Do not count subject in the denominator for "Urine RBC

				(Hematuria, Quantitative or Dipstick)"

BL = Baseline. Quant = Quantitative. "-" means any value can be present (or it can be missing), as it does not affect the classification

18) 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 7.4.2)

19) Lipid modifying medication analyses:

- Lipid modifying medication is defined to be the concomitant medication with WHO Drug ATC2 term (drug class) = "LIPID MODIFYING AGENTS" and WHO Drug preferred drug name (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 dose date) for randomized phase analysis.

  a) More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in safety analysis set for randomized phase analysis with meeting both the following criteria: 1) any selected CM record with the start date ≤ the first dose date for randomized phase analysis, and 2) the end date of the selected CM record ≥ the first 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 first dose date, lipid modifying medication was considered as being taken at study entry if the end date is not prior to the first dose date (ie, the end date is on or after the first dose date, completely unknown, or ongoing).

  c) Lipid modifying medications with the start date prior to the first dose date for randomized phase analysis 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 dose date).

- Subjects who initiated lipid modifying medications during the study for randomized phase analysis refer to the subjects in the safety analysis set who didn't take lipid modifying medications at study entry and with any selected CM record started after the first blinded study drug dose date and on and prior to the last blinded study drug dose date.

- Subjects who took lipid modifying medications at first dose of B/F/TAF (including both phases) refer to the subjects who use of the lipid modifying agents at study day 1 of all B/F/TAF analysis. More specifically, subjects with "Lipid Modifying Agent Use at

First Dose of B/F/TAF" include those subjects in All B/F/TAF Analysis Set with: 1) any selected CM record with the start date ≤ the first dose date of B/F/TAF (including both phases), and 2) the end date of the selected CM record is ongoing or the end date of the selected CM record ≥ the first dose date of B/F/TAF (including both phases).

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

b) Lipid modifying medications with the start date on or prior to the first dose date of B/F/TAF (including both phases) and the end date completely unknown were considered as being taken at first dose of B/F/TAF (including both phases).

- Subjects who initiated lipid modifying medications while subject receiving B/F/TAF includes the following subjects in the All B/F/TAF Analysis Set: (1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date of B/F/TAF (including both phases) and on or prior to last dose of B/F/TAF (including both phases). (2) for subjects who meet criteria (1) above, if they took lipid modification medications at first dose of B/F/TAF (including both phases), or if they took lipid modifying medications on or after randomized phase first dose and before first dose of B/F/TAF, they will NOT be considered initiated lipid modifications while receiving B/F/TAF for the all B/F/TAF analysis.

20) 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.

21) Vital signs and weight, height, BMI will be in the same listing.

22) HIV/HBV and HIV/HCV Coinfection:

- The following table presents the HBV and HCV tests with all possible values. Values that have an asterisk after them denote a "positive" (or "quantifiable" for HBV DNA and HCV RNA) result while all others denote a "negative" result.

Label	LBTESTCD	LBTEST	Possible Values
HBsAg	ATT1	Hep.B Surf.Ag Quant(-70)CL	NUMERICAL VALUE or "<0.05" or ">124925.00" (IU/mL)
HBsAg	ATT2	Hep. B Surf. Ag Qual(-70)-CL	"Repeat reactive, confirmed"*, "Repeat Reactive Unconfirmed", "Non-Reactive"
HBsAb	CNT353	anti-Hep B Surface Ag2 Qual	"Positive"*, "Negative"
HBcAb	CNT68	Hepatitis B Core Total	"Positive"*, "Negative"
HBV DNA	GET1883	HBV DNA CAP/CTM 2.0-EDTA-CL	"No HBV DNA detected", "<20 IU/mL HBV DNA detected", ">170000000"*, NUMERICAL VALUE (IU/mL)*
HBV DNA	GET1884	HBV DNA CAP/CTM 2.0Dil-EDTA-CL	NUMERICAL VALUE (IU/mL)*
HCVAb	CNT350	Hepatitis C Virus Antibody	"Positive"*, "Indeterminate", "Negative"
HCV RNA	GET1881	HCV RNA CAP/CTM 2.0EDTA-CL	"No HCV RNA detected", "<15 IU/mL HCV RNA detected", NUMERICAL VALUE (IU/mL)*

Note: HBVDNA AMPLIPREPTAQMAN 2.0 DIL(GET1884) is for HBV DNA CAP/CTM 2.0 >170,000,000 IU/mL. HBsAg(ATT1) test is conducted when HBsAg(ATT2) when ATT2 results = "Repeat reactive, confirmed", "Repeat Reactive Unconfirmed".Only HBsAg (ATT2) results will be summarized for HBV surface antigen.

- For baseline coinfection, when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date defined for randomized phase analysis or all B/F/TAF analysis for each test (eg, HBsAg, HBsAb, HBcAb, and HBV DNA)

  — The baseline coinfection status will be one of the three values: Yes/No/Null

  — The following tables provide combinations of HBV and HCV tests and the corresponding baseline coinfection status

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive	-	-	-	Y
Negative	Positive	-	-	N
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
	Missing	Positive	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
Missing	Positive	-	-	Null
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	Null
			Missing	Null
		Negative	-	Null
		Missing	-	Null
	Missing	-	-	Null

HCVAb	HCV RNA	Coinfection Status
Positive	Quantifiable	Y
	Not Quantifiable	N
	Missing	Null
Negative	-	N
Missing	Quantifiable	Null
	Not Quantifiable	N
	Missing	Null

"-" means any value can be present, as it does not affect the classification

- For incident coinfection, all laboratory tests must share the same accession number and if any set of values meets the criteria, then the subject is considered to have incident coinfection

  — The incident coinfection status will be one of two values: Yes/Null

  — The following tables provide combinations of HBV and HCV tests that are considered "Y" for incident coinfection status (all others are considered Null)

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive	-	-	-	Y
Negative	Negative	Positive	Quantifiable	Y
Missing	Negative	Positive	Quantifiable	Y

HCVAb	HCV RNA	Coinfection Status
Positive*	-	Y
-	Quantifiable	Y

* Subjects with positive HCVAb postbaseline must also have negative or missing HCVAb at baseline in order to be considered as having incident HIV/HCV coinfection.
"-" means any value can be present, as it does not affect the classification

— For adverse events, the start date must be after the first dose date and on or prior to the last dose date for randomized phase analysis.

— For incomplete AE start dates, please follow the logic specified in Section 7.1.5.2, but modify the second criterion to read, "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 of the last dose of study drug for randomized phase analysis".

23) HBV DNA test codes: If the result of the laboratory test code GET1883 (HBV DNA CAP/CTM 2.0-EDTA-CL) is listed as ">170000000", then a reflexive test code GET1884 (HBV DNA CAP/CTM 2.0Dil-EDTA-CL) should be performed and will share the same accession number as the original GET1883 test. In this instance, use the result from GET1884 instead of GET1883 when determining HBV DNA.

24) Reasons for Subjects who excluded from Week 48 PP Analysis Set will be summarized as follows in table:

a) Did Not Have On-Treatment HIV-1 RNA in Week 48 Window Unless due to Discontinuation of Study Drug for Lack of Efficacy

b) Did Not Meet the Criteria of Taking DTG + F/TAF, or DTG + F/TDF for the Protocol-defined Duration Before the screening visit

c) Did Not Meet the Criterion of HIV-1 RNA < 50 copies/mL for the Protocol-defined Duration Before screening visit

d) Did Not Meet the Criteria of HIV-1 RNA < 50 copies/mL at screening visit

e) Did Not Meet the Criteria of Having no Resistance to INSTIs or Confirmed Virologic Failure

f) Did Not Meet the Criteria of Having only the Protocol Permitted Historical ARV resistance

g) Took Protocol Prohibited Medications

h) Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile

25) The number of decimal places in reporting p-values should be as follows:

a) values less than 0.0001 → < 0.0001

b) values greater than 0.0001 → round to 4 decimal places

26) In this study, only 3rd generation LDL is collected.

27) For nonstudy-drug ARV listing, ARVs which were dosed between the first dose date and the last dose date (inclusive) of study will be flagged (eg, ^). However, please note, if CM end date is completely missing and it's not ongoing and CRF said it's a 'Prior ARV', the ARV will not be flagged.

28) Study and/or study drug discontinuations due to COVID-19

a) Study Drug Discontinuation

- Run NLP algorithm on the comment field from Study Drug Completion eCRF, checking for "COVID-19" text
- In COCOVID19 data set if COFORM = "Study Drug Completion" , then subject discontinued study drug due to COVID-19
- If study drug discontinued due to an AE, check if corresponding AE flagged as a COVID-19

b) Study Discontinuation

- Run NLP algorithm on the comment field from general comments for "COVID-19" text
- In COCOVID19 data set if COFORM = "Study Completion", then subject discontinued study due to COVID-19
- If study discontinued due to an AE, check if corresponding AE flagged as a COVID-19

29) Serum Creatinine and eGFR correction

a) Serum creatinine (corrected)

For serum creatinine, the calibrator lot used in the quantitative assay for the measurement of serum creatinine was changed globally on 01JUL2018 local time. Each regional lab center conducted its own alternate (quantitative) method comparison, comparable results as noted in the table below.

- For test results reported (RPTDTM) on or after 01JUL2018, use the inverse conversion formula in the below table as Calibration lot changed on 01JUL2018 local time.

- The correction is based on unit of umol/L, after correction by regular regression, covert to mg/dL by multiplying 0.0113.

Regional Lab Center	Accession Number	Regular Regression for Correction (umol/L)	Inverse Conversion Formula (umol/L)
Indianapolis	start with 65	Y=1.002*X+1.77	Y=(X-1.77)/1.002
Geneva	start with 62 or 63	Y=1.025*X+2.62	Y=(X-2.62)/1.025
Shanghai	start with 67	Y=0.971*X+5.42	Y=(X-5.42)/0.971
Singapore	start with 64 or 66	Y=1.009*X-1.42	Y=(X+1.42)/1.009
Japan	start with 68	Y=1.033*X+7.25	Y=(X-7.25)/1.033

Accession numbers specified which regional lab center tested the sample. For example, samples with accession number started with 65 were tested in Indianapolis Auto Chemistry Center.

b) eGFR (corrected)

Recalculate eGFR using the corrected serum creatinine, using the following formula: eGFRCG (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, age refers to the age at the sample collection date.

30) After Day 1, calcium, phosphorous, and magnesium tests were not performed unless a retest was needed so there is no summary table provided for these laboratory tests.

GS-US-380-4030 Final Analysis SAP V1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	30-Apr-2021 21:44:20
PPD	Clinical Research eSigned	04-May-2021 04:00:46