STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Fixed Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment Naïve, HIV-1 and Hepatitis B Co-Infected Adults
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF; GS-9883/F/TAF)
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
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
CG	Cockcroft-Gault
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
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
ID	identification
IDMC	independent data monitoring committee
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PK	pharmacokinetic
PP	per protocol
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
RNA	ribonucleic acid
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFL	tables, figures, and listings
TFV	tenofovir
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 the final analysis for Study GS-US-380-4458, which will be performed when all participants have completed the study or prematurely discontinued from the study drug. This SAP is based on the study protocol amendment 2 dated 06 July 2018 and the electronic case report form (eCRF). The SAP will be finalized before database finalization for the interim analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objectives of this study are:

- To evaluate the efficacy of fixed dose combination (FDC) of bictegravir /emtricitabine /tenofovir alafenamide (BIC/FTC/TAF; B/F/TAF) versus a regimen of dolutegravir (DTG) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; F/TDF) in HIV and HBV treatment naïve, HIV-1 and HBV co-infected participants as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF in HIV and HBV treatment naïve, HIV-1 and HBV co-infected participants as determined by the proportion of participants with plasma HBV DNA < 29 IU/mL at Week 48

The secondary objectives of this study are:

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 96

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of participants with plasma HBV DNA < 29 IU/mL at Week 96

- To evaluate the efficacy of the FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of participants with ALT normalization at Weeks 48 and 96

- To evaluate the efficacy of FDC of B/F/TAF versus DTG + F/TDF as determined by the proportion of participants with HBsAg loss at Weeks 48 and 96

- To evaluate the safety and tolerability of the two treatment groups through Week 96

1.2. Study Design

Design Configuration and Participant Population

Study GS-US-380-4458 is a randomized, double-blinded, multicenter, active-controlled study to evaluate the safety and efficacy of B/F/TAF FDC versus DTG + F/TDF FDC in treatment-naïve, HIV-1 and HBV co-infected adult participants.

Treatment Groups

Participants 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 (n=120):** FDC of BIC 50 mg/FTC 200 mg/ TAF 25 mg + placebo to match DTG 50 mg + placebo to match FDC of FTC 200 mg/TDF 300 mg administered orally, once daily, without regard to food
- **Treatment Group 2 (n=120):** DTG 50 mg + FDC of FTC 200 mg/TDF 300 mg + placebo to match FDC of B/F/TAF administered orally, once daily, without regard to food

Key Eligibility Criteria

Participants must meet ***all*** of the following inclusion criteria to be eligible to participate in the study:

- HIV-1 co-infection:
  1) Must be HIV antiretroviral treatment naïve with plasma HIV-1 RNA ≥ 500 copies/mL at screening
  2) ≤ 10 days of prior therapy with any antiretroviral agent, including lamivudine and entecavir, following a diagnosis of HIV-1 infection (except the use for PrEP or PEP, up to one month prior to screening)
  3) Screening genotype report must show sensitivity to FTC and TFV. This report will be provided by Gilead Sciences. Alternatively, if genotype results from a local laboratory obtained ≤ 90 days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed
- HBV co-infection:
  4) Must be HBV treatment naïve (defined as < 12 weeks of oral antiviral treatment)
  5) Screening HBV DNA ≥ 2,000 IU/mL
- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault (C-G) formula (at the screening visit)

Study Periods/Phases

After screening, eligible participants will be treated for at least 96 weeks during the blinded treatment phase. Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 8, 12 and every 12 weeks thereafter.

Once all participants complete their Week 96 visit and Gilead completes the Week 96 analysis, all participants 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 the B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected participants following review of unblinded data, participants in a country where the B/F/TAF FDC is not available will be given the option to receive the B/F/TAF FDC in an open label (OL) extension phase for up to 48 Weeks or until the product becomes accessible to participants through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

All participants 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.

Participants who complete the study through the End of Blinded Treatment Visit and do not continue on the OL 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 participant completing the End of Blinded Treatment Visit.

Schedule of Assessments

After screening procedures, eligible participants will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 96 weeks. Following the Day 1 visit, participants will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks from Week 12 through Week 96. After Week 96, all participants will continue to take their blinded study drugs and attend a study visit every 12 weeks until the End of Blinded Treatment Visit.

Laboratory analyses (serum chemistry, liver function tests, hematology, urinalysis, pregnancy testing [for females of childbearing potential]), will be performed at the Screening, Day 1, and all subsequent study visits. HIV-1 RNA and CD4 + cell count will be performed at Screening, Day 1, and all subsequent study visits. HIV-1 genotype (RT and PR) will be determined at screening. Plasma HBV DNA levels, HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab) will be performed at Screening, Day 1, and every 12 weeks thereafter. Plasma HBV DNA will be monitored at all study visits.

Serum samples for potential sequence analysis of HBV polymerase/reverse transcriptase (pol/RT) should be collected at all time points except screening. Sequencing analysis of the HBV pol/RT will be attempted for all viremic participants (HBV DNA > 69 IU/mL) at Weeks 48, 96 or early study drug discontinuation as early as Week 8, as well as all participants who meet virologic breakthrough criteria.

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

More details for study procedures may be found in Appendix 1.

Pharmacokinetics

A blood sample for pharmacokinetics (PK) trough analysis will be obtained 20 to 28 hours following the last dose at Weeks 4, 12, and 36. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours postdose at Weeks 8 and 24.

Randomization

Participants 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 HBeAg (positive vs negative), HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL), CD4+ cell count (< 50 cells/μL vs ≥ 50 cells/μL) at screening.

Site and/or Stratum Enrollment Limits

Approximately 70 study sites worldwide participated. There was no enrollment limit for individual sites.

Study Duration

The randomized, double-blind phase of this study is at least 96 weeks in duration.

1.3. Sample Size and Power

A total of approximately 240 HIV-1 and HBV co-infected participants, randomized in a 1:1 ratio to 2 treatment groups (120 participants per treatment group), achieves 90% power to detect a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA-defined snapshot algorithm) difference between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have a response rate of 91% (based on Gilead Studies GS-US-380-1489 and GS-US-380-1490), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

A total of approximately 240 participants also provides 81% power to detect a non-inferiority margin of 12% with respect to the co-primary efficacy endpoint of the proportion of participants with plasma HBV DNA < 29 IU/mL at Week 48. This assumes that both treatment groups have a response rate of 88% (based on Gilead Studies GS-US-320-0108 and GS-US-320-0110), that the non-inferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

The Week 24 Independent Data Monitoring Committee (IDMC) analysis was conducted after all participants enrolled completed their Week 24 visit or prematurely discontinued from 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.

2.2. Interim Analyses

2.2.1. Week 48 Analysis

The Week 48 analysis was conducted after all participants either completed their Week 48 visit or prematurely discontinue from the study drug.

2.2.2. Week 96 Analysis

The Week 96 analysis was conducted after all participants either completed their Week 96 visit or prematurely discontinued from the study drug.

2.2.3. Final Analysis

The final statistical analysis will be conducted after all participants either complete the study or prematurely discontinue from 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 analysis: randomized phase analysis and all B/F/TAF analysis. All table summaries in this final analysis will be based on data included in the All B/F/TAF analysis (eg, data collected during the study period when participants were on B/F/TAF).

Randomized phase analysis (eg, including data collected during double-blind phase when participants were on the double-blind study drug), and the corresponding analysis window defined in Section 3.8, will be used to support applicable listings where data collected from the double-blind phase are indicated. The wording of randomized phase or double-blind phase might be used interchangeably throughout the SAP and in the TFLs.

Randomized Phase Analysis:

- For participants who are never treated in the extension phase of the study, including those who prematurely discontinue the randomized study drug or who complete the randomized study drug 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 participants 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 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, electrocardiogram (ECG), collected on or prior to the extension phase first dose date.

All B/F/TAF Analysis:

- For participants who receive B/F/TAF in the randomized phase, all available data for participants who actually receive B/F/TAF in the randomized phase will be included.

- For participants who actually receive DTG + F/TDF 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. 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 participants who actually receive DTG + F/TDF 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 participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

For the All B/F/TAF analysis, no statistical comparison between treatment groups will be conducted.

By-participant listings will be presented for all participants in the all randomized analysis set unless otherwise specified, and sorted by participant ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a participant. The treatment group to which participants were randomized will be used in the listings. Most listings will be provided for the all randomized analysis set for data from both phases of the study. Some listings for the all B/F/TAF safety analysis set will also be provided.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. For randomized but never dosed participants, 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 randomized study drug refers to premature discontinuation of the randomized study drug or completion of the randomized 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 randomized study drugs (B/F/TAF or DTG + F/TDF); for the all B/F/TAF analysis, study drug refers to B/F/TAF.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of participants in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

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

3.1.2. All B/F/TAF Full Analysis Set

The **All B/F/TAF Full Analysis Set** will include all participants who (1) are randomized into the study, (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, and (3) have at least 1 post baseline HIV-1 RNA or HBV DNA results while on B/F/TAF. This is the primary analysis set for the all B/F/TAF efficacy analyses.

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

3.1.3. All B/F/TAF Safety Analysis Set

The **All B/F/TAF Safety Analysis Set** will include all participants who (1) are randomized into 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 safety analyses.

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

3.1.4. All B/F/TAF Serologically Evaluable Full Analysis Set

3.1.4.1. All B/F/TAF Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion

The All B/F/TAF Serologically Evaluable Full Analysis Set for HBsAg loss/seroconversion includes all participants who were in the All B/F/TAF Full Analysis Set, and with HBsAg positive and HBsAb negative or missing at baseline.

3.1.4.2. All B/F/TAF Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion

The All B/F/TAF Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion includes all participants who were in the All B/F/TAF Full Analysis Set, and with HBeAg positive and HBeAb negative or missing at baseline.

3.2. Participant Grouping

For analysis using the All Randomized Analysis Set, participants will be grouped by the randomized treatment (labeled as B/F/TAF vs. DTG + F/TDF).

For all analyses included in the all B/F/TAF analysis, participants will be grouped into the following 2 groups:

- B/F/TAF group: This group includes all participants who actually received B/F/TAF in the randomized phase of this study, regardless whether participants receive any B/F/TAF in the extension phase or not.
- DTG + F/TDF to B/F/TAF group: This group includes all participants who actually received DTG + F/TDF regimen in the randomized phase of this study and then receive at least 1 dose of B/F/TAF in the extension phase.

3.3. Strata and Covariates

Randomization was stratified by HBeAg (positive vs. negative), HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL), CD4+ cell count (< 50 cells/μL vs ≥ 50 cells/μL) at screening.

3.4. Examination of Participant Subgroups

3.4.1. Participant Subgroups for Safety Analyses

Selected safety endpoints (eg. AEs and liver-related laboratory tests) may be analyzed for the following participant subgroups (see Section 8.1 for details):

- Participants with HIV/HBV/hepatitis C virus (HCV) coinfection at baseline
- Participants with incident HIV/HBV/HCV coinfection while on study drug (if any)

3.5. Multiple Comparisons

No alpha level adjustment is applied other than for the primary endpoints at Week 48.

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 participant 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 medications in Section 7.5.

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

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

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

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data 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).

For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios.

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 cp/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. For the Cobas 6800 Assay for HBV DNA, "<10 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 9 IU/mL for analysis purposes.

For data from a local laboratory, data would be treated as missing data if its reported unit is missing but its corresponding unit from a central laboratory is not missing, or its reported unit is not missing but a value in conventional unit is missing (due to no confirmed unit conversion formula available).

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 study drug (ie, B/F/TAF, DTG +F/TDF) was taken, as recorded on the Study Drug Administration eCRF.

Last Dose Date for the Randomized Phase analysis is the latest of the blinded study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug in the "Blinded Treatment" study phase according to the Study Drug Completion eCRF.

If last dose date for the Randomized Phase 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 randomized study drug start dates and end dates, or the latest clinical visit dates and the laboratory visit dates prior to the first dose date of B/F/TAF in the extension phase (if applicable), excluding the date of 30-day follow-up visit, will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications for imputation rule details.

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

- For participants 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 participants who actually received DTG + F/TDF 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/TDF 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, 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 phases) end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug in either or both of the study phases ("Blinded Treatment", "Open-Label Treatment") according to the Study Drug Completion eCRF.

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 phases) 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 either the randomized phase analysis or the all B/F/TAF analysis, as appropriate. For events that occurred on or after the Study Day 1 date of either analysis, study days are calculated as (visit date minus the date of 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 the date of Study Day 1.

Last Study Date is the latest of the study drug (including B/F/TAF and DTG + F/TDF in both phases) 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 either the randomized phase analysis or the all B/F/TAF analysis, as appropriate. Participants who actually received DTG + F/TDF in the randomized phase and received at least 1 dose of B/F/TAF in extension phase will have a new baseline value for the All B/F/TAF analysis.

3.8.2. Analysis Windows

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

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

Table 3-1. Analysis Windows for HIV-1 RNA, HBV DNA, CD4+ cell count, CD4%, Hematology, Chemistry, Urinalysis, and Serum/Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, Weight and BMI for the 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 96	672	631	714
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

Table 3-2 Analysis Windows for HIV-1 RNA, HBV DNA, CD4+ cell count, CD4%, Hematology, Chemistry, Urinalysis, and Serum/Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, Weight and BMI for the All B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TDF 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.
Note: For the DTG + F/TDF 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 the previous visit.

The analysis windows for HBV serology (including HBsAb, HBsAg, hepatitis B e-antigen [HBeAg], and hepatitis B e-antibody [HBeAb]) are presented in Table 3-3 and Table 3-4.

Table 3-3. Analysis Windows for HBV Serology for the Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	756
Week K (K is every 24 weeks after Week 96)	K*7	(K-12)*7+1	(K+12)*7

Table 3-4. Analysis Windows for HBV Serology for the All B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TDF 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	210	NA	NA	NA
Week 36	252	211	294	NA	NA	NA
Week 48	336	295	378	336	2	504
Week 60	420	379	462	NA	NA	NA
Week 72	504	463	546	NA	NA	NA
Week 84	588	547	630	NA	NA	NA
Week 96	672	631	756	672	505	840
Week K	K*7	(K-12)*7+1	(K+12)*7	NA	NA	NA

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.
Note: For the DTG + F/TDF 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 in blinded phase and every 48 weeks in OL extension phase.

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 3-5 and Table 3-6.

Table 3-5 Analysis Windows for Metabolic Assessments for the Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week K (K is every 24 weeks after previous visit)	K*7	(K-12)*7+1	(K+12)*7

Table 3-6 Analysis Windows for Metabolic Assessments for All B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TDF to B/F/TAF		
Visit ID	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 24	168	2	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.
Note: For the DTG + F/TDF 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 renal function (including urine RBP and urine beta-1-microglobulin) are presented in Table 3-7.

Table 3-7 Analysis Windows for Renal Function for the Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	504
Week 96	672	505	756

The analysis windows for HCV serology is presented in Table 3-8 and Table 3-9.

Table 3-8 Analysis Windows for HCV Serology and HCV RNA for the Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week 96	672	505	840
Week K (K is every 48 weeks after previous visit)	K*7	(K-24)*7+1	(K+24)*7

Table 3-9 Analysis Windows for HCV Serology and HCV RNA Assessments for the All B/F/TAF Analysis

	B/F/TAF Group			DTG + F/TDF 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.
Note: For the DTG + F/TDF 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.

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 will be selected. If there are multiple records with the same time or no time recorded on the same day, an average will be used for the baseline value, except for HIV-1 RNA (see below).

- For postbaseline visits:
  - For CD4+ cell count and CD4%, the record(s) collected on the latest day in the window will be selected for analysis.
  - For ALT, the record with the largest value in the window will be selected.
  - For HBV DNA, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the geometric mean will be taken.
  - For other numeric observations (ie, except HIV-1 RNA, ALT, HBV DNA, CD4+ cell count, and CD4%), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.
  - For any numeric observations except HIV-1 RNA, ALT, and HBV DNA, 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" (or "HIV-1 RNA Expedited" from China) 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" (or "HIV-1 RNA Expedited" from China) records with the same collection time, the geometric mean will be taken for analysis purposes.

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

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).
- For postbaseline visits, the most conservative value within the window will be selected.
- For HBeAg, HBeAb, HBsAg, and HBsAb, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the most conservative value will be taken, ie, positive will be selected over negative for HBeAg and HBsAg, and negative will be selected over positive for HBeAb and HBsAb.

In an analysis window (including baseline window), if both central lab and local lab results are available, then central lab results will be used for record selection instead of local lab results; local lab results will only be used for record selection if central lab results are missing.

4. SUBJECT DISPOSITION

4.1. Participant Enrollment and Disposition

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

4.1.1. Participant Enrollment

All necessary summaries on participant enrollment have been performed as part of the Week 48 analysis, and will not be repeated for the final analysis.

4.1.2. Participant Disposition

The summary of participant disposition will be provided by treatment group and overall for all randomized participants. This summary will include participants randomized, participants randomized but never treated, participants in the Safety Analysis Set, and participants in the FAS.

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

- Participants completing study drug in the randomized phase
- Participants prematurely discontinuing study drug in the randomized phase (with summary of reasons for discontinuing study drug in the randomized phase)
- Participants completing study in the randomized phase
- Participants prematurely discontinuing from study in the randomized phase (with summary of reasons for discontinuing from study in the randomized phase)
- Participants entering the OL extension phase
- Participants treated in the OL extension phase
- Participants 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)
- Participants 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 participants in each category in the randomized phase, including "Participants entering the OL extension phase", will be the number of participants randomized and treated in the randomized phase. The denominator for the percentages of participants in each category in the OL extension phase will be the number of participants who were treated in OL extension phase.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided. 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 the all B/F/TAF 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 phase 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 (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants 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 (756 days), ≥ 120 weeks (840 days), ≥ 132 weeks (924 days), ≥ 144 weeks (1008 days), etc.

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

Time to premature discontinuation of study drug will be analyzed by treatment group using the Kaplan-Meier (KM) method for 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 premature discontinuation of study drug by treatment group will be generated for the All B/F/TAF analysis. Participants who completed study drug will be censored at the last dose data of the study.

4.2.2. Adherence to Study Drug Regimen

Adherence to study drug regimen will be defined for the all B/F/TAF analysis. For all B/F/TAF analysis, study drug adherence (for B/F/TAF) will be computed for both treatment groups as defined in Section 3.2. Study drug regimen adherence will be computed based on pill counts. 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:

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

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

[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 the all B/F/TAF analysis. Overall adherence for the all B/F/TAF analysis will use all available data for participants 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 participants 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 a study drug regimen (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for participants who return at least 1 bottle of randomized study drug, and who have calculable adherence for the All B/F/TAF Analysis Set. No inferential statistics will be provided.

4.3. Protocol Deviations

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

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic, which had an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis. Data collection and determination of COVID-19 data are described in Appendix 5.

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

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

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

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

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 5.

4.4.4. Adverse Events Due to COVID-19

Adverse events of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic 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 participants for categorical data. The summaries of demographic data and baseline characteristics will be provided by treatment groups for participants in the All B/F/TAF Safety Analysis Set (noticing that the baseline for all B/F/TAF analysis will be adjusted based on first dose of B/F/TAF), respectively.

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

5.2. Baseline Disease Characteristics

5.2.1. HIV Baseline Characteristics

The following HIV baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for the All B/F/TAF analysis:

- HIV-1 RNA (log_{10} copies/mL)
- HIV-1 RNA categories (copies/mL): (a) ≤ 100,000, (b) > 100,000 to ≤ 400,000, and (c) > 400,000
- 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)
- HIV disease status
- $eGFR_{CG}$ (mL/min)

5.2.2. HBV Baseline Characteristics

The following HBV baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for the All B/F/TAF analysis:

- HBV DNA (log_{10} IU/mL)
- HBV DNA categories (IU/mL): (a) < 7 log_{10}, (b) ≥ 7 log_{10} to < 8 log_{10}, and (c) ≥ 8 log_{10}
- ALT (U/L)
- ALT category (ULN) based on central laboratory normal range: (a) ≤ 1, (b) > 1 to ≤ 5, (c) > 5 to ≤ 10, and (d) > 10
- ALT category (ULN) based on American Association for the Study of Liver Diseases (AASLD) normal range with the ULN as 25 U/L for female and 35 U/L for male: (a) ≤ 1, (b) > 1 to ≤ 5, (c) > 5 to ≤ 10, and (d) > 10
- Hepatitis B surface antigen status
- Hepatitis B surface antibody status
- Hepatitis B e-antigen status
- Hepatitis B e-antigen and HBV DNA stratum: (a) Positive and ≥ 8 log_{10} IU/mL, (b) Negative and ≥ 8 log_{10} IU/mL, (c) Positive and < 8 log_{10} IU/mL, and (d) Negative and < 8 log_{10} IU/mL
- Hepatitis B e-antibody status
- Hepatitis C antibody status
- HIV/HBV/HCV Coinfection (see definition in Section 8.1)
- HBV Genotype Group (A, B, C, D, E, F, etc.)
- Mode of infection (HBV risk factor)
- Years positive for HBV (Years since participant was first documented to be HBV positive)

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

5.3. Medical History

A listing of general medical history data will be provided.

General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

6. EFFICACY ANALYSES

All necessary summaries on the primary efficacy endpoint (at Week 48) and the secondary endpoints at Weeks 48 and 96 have been performed as part of the Week 48 CSR and Week 96 CSR, and will not be repeated for the final analysis.

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of participants 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 purposes.

The co-primary efficacy endpoint is the proportion of participants with plasma HBV DNA < 29 IU/mL at Week 48 as defined by Missing = Failure (M = F) approach.

The statistical analysis methods for the primary and co-primary efficacy endpoints were described in the Week 48 SAP and the analyses were performed in the Week 48 analysis, and will not be repeated for the final analysis.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoints

6.2.1.1. Secondary HIV Efficacy Endpoints

The secondary HIV efficacy endpoints include:

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 96 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count and CD4% at Weeks 48 and 96

6.2.1.2. Secondary HBV Efficacy Endpoints

The secondary HBV efficacy endpoints include:

- The proportion of participants with plasma HBV DNA < 29 IU/mL at Week 96
- The proportion of participants with ALT normalization at Weeks 48 and 96
- The proportion of participants with HBsAg loss at Weeks 48 and 96

Both baseline and postbaseline non-reactive HBV serology results will be imputed as negative, and reactive results will be imputed as positive.

The statistical analysis methods for the secondary efficacy endpoints at Weeks 48 and 96 (based on data included in the randomized phase analysis) were described in the previous interim analyses SAPs and the analyses were performed in the previous interim analyses.

6.3. Other Efficacy Endpoints for all B/F/TAF Analysis

6.3.1. Definition of the Other Efficacy Endpoint for all B/F/TAF analysis

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

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 144 (OL Week 48) by M = E approach
- The change from baseline in CD4+ Cell Count and CD4 percentage (%) at Week 144 (OL Week 48)

The analyses for these efficacy endpoints above will be conducted based on the All B/F/TAF Full Analysis Set.

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

- The proportion of participants with plasma HBV DNA < 29 IU/mL at Week 144 (OL Week 48) by M = E approach
- The proportion of participants with ALT normalization at Week 144 (OL Week 48) by M = E approach
- The proportion of participants with normal ALT at Week 144 (OL Week 48) by M = E approach
- The proportion of participants with HBsAg loss at Week 144 (OL Week 48) by M = E approach

  This is defined as HBsAg test result changes from HBsAg positive at baseline to HBsAg negative at a given postbaseline visit with baseline HBsAb negative or missing.
- The proportion of participants with HBsAg seroconversion to anti-HBs at Week 144 (OL Week 48) by M = E approach

  This is defined as HBsAg loss and HBsAb test result changes from HBsAb negative or missing at baseline to HBsAb positive at a given postbaseline visit.
- The proportion of participants with HBeAg loss at Week 144 (OL Week 48) by M = E approach

This is defined as HBeAg test result changes from HBeAg positive at baseline to HBeAg negative at a given postbaseline visit with baseline HBeAb negative or missing.

- The proportion of participants with HBeAg seroconversion to HBeAb at Week 144 (OL Week 48) by M = E approach

  This is defined as HBeAg loss and HBeAb test result changes from HBeAb negative or missing at baseline to HBeAb positive at a given postbaseline visit.

6.3.2. Analysis of Other Efficacy Endpoints for All B/F/TAF Analysis

6.3.2.1. Analysis of the Proportion of Participants with HIV-1 RNA < 50 copies/mL by Missing = Excluded Approaches

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

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

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

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

For all B/F/TAF analyses, the 95% CI for the proportion of participants with HIV-1 RNA < 50 copies/mL for a treatment group will be constructed using the Clopper-Pearson exact method.

For the M = E analysis, results will be summarized by treatment group for all visits through the end of study. No statistical comparison will be made for the all B/F/TAF analysis.

6.3.2.2. 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 Full 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 Full 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 while receiving B/F/TAF will be plotted.

6.3.2.3. Analysis of the Proportion of Participants with plasma HBV DNA < 29 IU/ by Missing = Excluded Approaches

The analysis of HBV DNA will be based on on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for participants who were still on study drug) for participants in the All B/F/TAF analysis.

In M = E approach, all missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the all B/F/TAF Full analysis set with nonmissing HBV DNA value at that visit.

For the M = E approach for HBV DNA, the number and percentage of participants with HBV DNA in the following categories will also be summarized by treatment group:

- < 29 IU/mL
  - < 20 IU/mL
    - < 20 IU/mL Not Detectable
    - < 20 IU/mL Detectable
  - ≥ 20 to < 29 IU/mL
- ≥ 29 IU/mL
  - ≥ 29 to < 69 IU/mL
  - ≥ 69 IU/mL

For all B/F/TAF analyses, the 95% CI for the proportion of participants with HBV DNA < 29 IU/mL for a treatment group will be constructed using the Clopper-Pearson exact method.

For the M = E analysis, results will be summarized by treatment group for all visits through the end of study. No statistical comparison will be made for the all B/F/TAF analysis.

6.3.2.4. Analyses of the other HBV Efficacy Endpoints involving Proportions

All the other HBV efficacy endpoints involving proportions will be based on on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for participants who were still on study drug) and will be analyzed using M = E methods.

For the M = E analysis, results will be summarized by treatment group for all visits through the end of study. No statistical comparison will be made for the all B/F/TAF analysis.

The other HBV efficacy endpoints involving proportions will be assessed using all B/F/TAF FAS except the following:

- the proportion of participants with HBsAg seroconversion to anti-HBs by visit will be evaluated using all B/F/TAF serologically evaluable FAS for HBsAg loss/seroconversion.
- the proportion of participants with HBeAg seroconversion to anti-HBs by visit will be evaluated using all B/F/TAF serologically evaluable FAS for HBeAg loss/seroconversion.

6.4. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the All B/F/TAF Safety Analysis Set for the all B/F/TAF analysis, unless specified otherwise. All safety data collected up to 30 days after permanent discontinuation of study drug B/F/TAF will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

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 phase 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-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if 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 Gilead Patient Safety (PS) 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.

For the all B/F/TAF analysis, the AE onset date will be compared with the first and last dose dates for the All B/F/TAF phase analysis.

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 and stop dates, 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 participants 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 using the All B/F/TAF Safety Analysis Set:

- 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 participants 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 participant 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 participant 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.

All treatment-emergent AEs by SOC and PT will be summarized by subgroups defined in Section 3.4.1.

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

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study Drug-Related SAEs
- Death 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 Protocol Appendix 7). 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. Hepatic Events

Preferred terms for defining 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 PS and reviewed by Gilead medical monitors (see details in Appendix 6).

The number and percentage of participants with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group based on the All B/F/TAF Safety Analysis Set. No statistical comparisons of the participant incidence rates between the 2 treatment groups will be performed. A data listing of hepatic events will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the All B/F/TAF Safety Analysis Set. 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-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the 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.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group 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 (yrs) × 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.

For baseline, if both central lab and local lab results are available, then central lab results will be used to determine baseline toxicity grade; local lab results will only be used if central lab results are missing. For postbaseline laboratory abnormalities, both central lab and local lab results will be used.

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 nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

For the International normalized ratio (INR) of prothrombin time (PT), protocol-specified toxicity grade scale depends on the upper limit of normal range (ULN). While the ULN of INR depends on whether the participant is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 – 1.2; Taking oral anticoagulant: 2.0 – 3.0), this information is not collected by the reference laboratory. As a result, INR will be graded by assuming the participant is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR. Consequently, INR and PT will not be included in summaries of laboratory abnormalities but will be included in listings for the following reasons: 1) INR and PT are reflexive tests; 2) only the absolute values, not the toxicity grade, are needed for participant management purposes; and 3) more importantly, the toxicity grades for INR may be over-reported.

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 or the last available date for participants who were still on study drug at the time of an interim analysis. 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. Notice that the baseline toxicity grade for all B/F/TAF analysis will be based on the first dose date of B/F/TAF.

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 participants; therefore, an abnormality is treatment-emergent or not cannot be determined for these participants.

Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed routinely and assigned a toxicity grade in this study. Urine RBC based on microscopic examination will be presented in laboratory toxicity summary tables and listings while urine blood based on a dipstick will be presented in the listings only.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab 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 participants with any nonmissing postbaseline values up to 30 days after last dosing date.

A by-participant listing of all laboratory abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by participant 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.

In addition, the number and percentage of participants who took lipid modifying medications at the first dose of B/F/TAF and initiated the medications while receiving B/F/TAF will be provided, respectively.

A lipid modifying medication is defined as a medication with drug class = "LIPID MODIFYING AGENTS" and CMDECOD containing the wording of "STATIN".

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

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 participants who were reported to have the following laboratory test values for postbaseline measurements (based on central laboratory normal range):

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

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, participants 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, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date. Participants 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.

7.2.5. ALT Elevation

An ALT elevation is defined as serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms. Confirmed ALT elevation (ALT flare) is defined as ALT elevations at 2 or more consecutive postbaseline visits. All treatment-emergent ALT elevations including confirmed ALT elevations will be summarized. Treatment-emergent ALT elevation is defined as ALT elevation at any postbaseline time point, up to 1 day after permanent discontinuation of study drug or the last available date for participants who were still on study drug. All treatment-emergent and nontreatment-emergent ALT elevations will be included in a listing.

7.2.6. Renal-Related Laboratory Evaluations

7.2.6.1. 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.

Median (Q1, Q3) of change from baseline in serum creatinine and $eGFR_{CG}$ over time will be plotted by treatment group.

7.3. Body Weight, Height, BMI and Vital Signs

Descriptive statistics will be provided by treatment group for vital signs, body weight and BMI as follows:

- 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.

Vital signs to be summarized include systolic, diastolic blood pressures (mmHg), pulse (beats/min), respiration (breaths/min), and temperature (C).

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

7.4. Non-Study Antiviral Medications

Non-study antiviral (including anti-retroviral and anti-hepatitis B) medications will be provided in a data listing using the safety analysis set.

7.5. Concomitant Non-Antiviral Medications

Concomitant non-antiviral medications (ie, medications other than study drug, and antiviral drugs that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 for All B/F/TAF analysis up to the date of last dose of study drug will be summarized (number and percentage of participants) by treatment group and generic name (preferred drug name). Multiple drug use will be counted only once per participant. The summary will be sorted by decreasing order of total frequency of medication generic name.

If the start or stop date of non-antiviral 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-antiviral medications 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-antiviral 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-antiviral medications are marked as ongoing and start date is on or before last dose date, the non-antiviral medications are concomitant.

Summaries of non-antiviral concomitant medications will be provided for the All B/F/TAF Safety Analysis Set. Participants with any non-antiviral concomitant medications will be listed. No inferential statistics will be provided.

7.6. Electrocardiogram Results

Electrocardiogram (ECG) is scheduled for screening only. A by-participant listing for ECG assessment results will be provided by participant ID number and visits in chronological order.

7.7. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study

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 using for the All B/F/TAF Safety Analysis Set only.

8.1. Analyses for HIV/HBV/HCV Coinfected Participants

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

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

Participants with incident HIV/HBV/HCV coinfection while on study drug B/F/TAF are defined as participants who are not HIV/HBV/HCV coinfected at baseline and meet any of the following criteria:

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

The following listings will be provided for participants with incident HIV/HBV/HCV coinfection while on B/F/TAF:

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

9. REFERENCES

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

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.) is to be used for 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

Appendix Table 1. Study Procedures Table (Blinded Phase)

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, q]										Post-Week 96[e, r]	End of Blinded Treatment Visit	30-Day Follow-up[p]	Early Study Drugs DC[c]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
Informed Consent	X															
Medical History	X															
Concomitant Medications	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[f]	X[f]
Complete/Symptom-Directed Physical Exam	X	X	X[d]	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X[d,f]	X[f]
12-Lead ECG (performed supine)	X															
Height	X															
Vital signs (blood pressure, pulse, respiration rate, and temperature), and Weight	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[f]	X[f]
Urine Sample for Markers of Renal Dysfunction		X				X		X				X				X
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[i]		X				X		X		X		X	X[i]	X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X
Hematology Profile[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and CD4%	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X	X	X
Blood Storage Samples[o]		X	X	X	X	X	X	X	X	X	X	X	X	X		X

Study Procedures	Screening[a]	Day 1[b]	End of Week[e, q]										Post-Week 96[e, r]	End of Blinded Treatment Visit	30-Day Follow-up[p]	Early Study Drugs DC[c]
			4	8	12	24	36	48	60	72	84	96	Every 12 Weeks			
HCV Serology[u]	X							X				X	X			
HIV-1 Genotype[k]	X															
HIV-1 Genotype/Phenotype[e]								X[e]				X[e]				X[e]
HBV Blood panel[t]	X	X			X	X	X	X	X	X	X	X	X[t]			
HBV Genotyping (A-H)		X														
Plasma HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum sample HBV Resistance Surveillance[w]		X	X	X	X	X	X	X[w]	X	X	X	X	X[w]	X	X	X[w]
Trough PK Blood Sample[l]			X		X		X									
Post-Dose PK Blood Sample[m]				X		X										
CCI																
Randomization[v]		X														
Provide participant dosing diary to participants		X	X	X	X	X										
Study Drug Dispensation		X[b]	X	X	X	X	X	X	X	X	X	X	X	X[s]		
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Administration of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit.
c Early Study Drugs Discontinuation visit to occur within 72 hours of last dose of study drug. Participants will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit even if the participant discontinues study drug during the blinded phase.
d Symptom-directed physical examination as needed. After Week 96 visit, complete physical exam to be completed every 48 weeks.
e HIV-1 genotype and phenotype of protease, reverse transcriptase, and integrase testing will be completed for participants with virologic failure. Following virologic rebound, participants 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 genotype and phenotype blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.14). Participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 and 96 will be asked to return for an unscheduled visit within the visit window for a retest. Participants with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit, Week 48 or 96 will also have resistance testing conducted.
f Any adverse event 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, or is otherwise explained.

g Females of childbearing potential only. Serum pregnancy testing will be performed at the Screening visit. Urine pregnancy testing will be performed at Day 1 and all subsequent study visits (except the 30 Day-Follow-up Visit). Positive urine pregnancy tests will be confirmed with a serum test.

h Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × ULN). At Day 1, Weeks 24, 48, 72, 96, every 24 weeks post Week 96, and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments every 24 weeks and not as part of the chemistry profile. PT/INR will be performed at Screening and Day 1.

i 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 participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments. After Week 96 Visit, metabolic assessments will be completed every 24 weeks.

j Complete blood count with differential and platelet count.

k The Investigator must have received the results from the screening HIV-1 genotype report before proceeding with the Day 1 visit. Screening HIV-1 genotype report must show sensitivity to TFV and FTC. If genotype results from a local laboratory obtained ≤ 90 days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed.

l Trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4, 12 and 36.

m Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose at Weeks 8 and 24.

n CD4+ cell count and CD4% to be completed at all study visits.

o Plasma and serum blood storage samples will be collected for safety, virology or PK testing. Whole blood storage samples will be collected for safety, virology or PK testing at Day 1, Week 48 and Week 96 visits.

p Only required for those participants who complete an End of Blinded Treatment Visit and do not wish to enroll in the open-label rollover extension or those participants who prematurely discontinue study drugs prior to the End of Blinded Treatment Visit and do not continue in the study through at least one subsequent visit after the Early Study Drugs Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.

q Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days through to Week 96, unless otherwise specified. The visit window at Weeks 48 and 96 will be ± 6 weeks of the protocol-specified visit date.

r After Week 96, all participants will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Visit window of ± 6 days for study visits post Week 96.

s Open label study drug, B/F/TAF FDC will be dispensed to participants participating in the Open-Label Rollover extension.

t HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab). After Week 96, HBV serology will be performed every 24 weeks.

u Hepatitis C virus (HCVAb) serology. Participants who are HCVAb positive will have a HCV RNA test performed. After Week 96 visit, testing to be performed every 48 weeks.

v 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 participant eligibility has been confirmed.

w Genotypic analysis of HBV polymerase/reverse transcriptase (pol/RT) for resistance surveillance will be attempted for all participants who remain viremic (HBV ≥ 69 IU/mL) at Week 48 and 96 (or early study drug discontinuation visit as early as Week 8) and for those with virologic breakthrough as defined in Protocol Section 6.15.

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

Study Procedures	Post End of Blinded Treatment Visit (every 12 weeks)[a,e,l]	30-Day Follow-up[k]	Early Study Drugs DC[c]
Adverse Events	X	X[f]	X[f]
Concomitant Medications	X	X	X
Complete/Symptom-Directed Physical Exam	X[d]	X[d,f]	**X**[f]
Vital signs (blood pressure, pulse, respiration rate, and temperature) and Weight	X	X	X
Urinalysis	X	X[f]	X[f]
Urine Pregnancy Test[g]	X		X
Chemistry Profile[h]	X	X[f]	X[f]
Metabolic Assessments[i]	X		
Estimated Glomerular Filtration Rate	X	X[f]	X
Hematology Profile[j]	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X
CD4+ Cell Count and CD4%	X	X	X
Blood Storage Sample[o]	X		X
HBV Blood Panel[m]	X[m]		
Plasma HBV DNA	X		
HCV Serology[n]	X[n]		
HIV-1 Genotype/Phenotype[e]			X[e]
Study Drug Dispensation[b]	X		
Study Drug Accountability	X		X

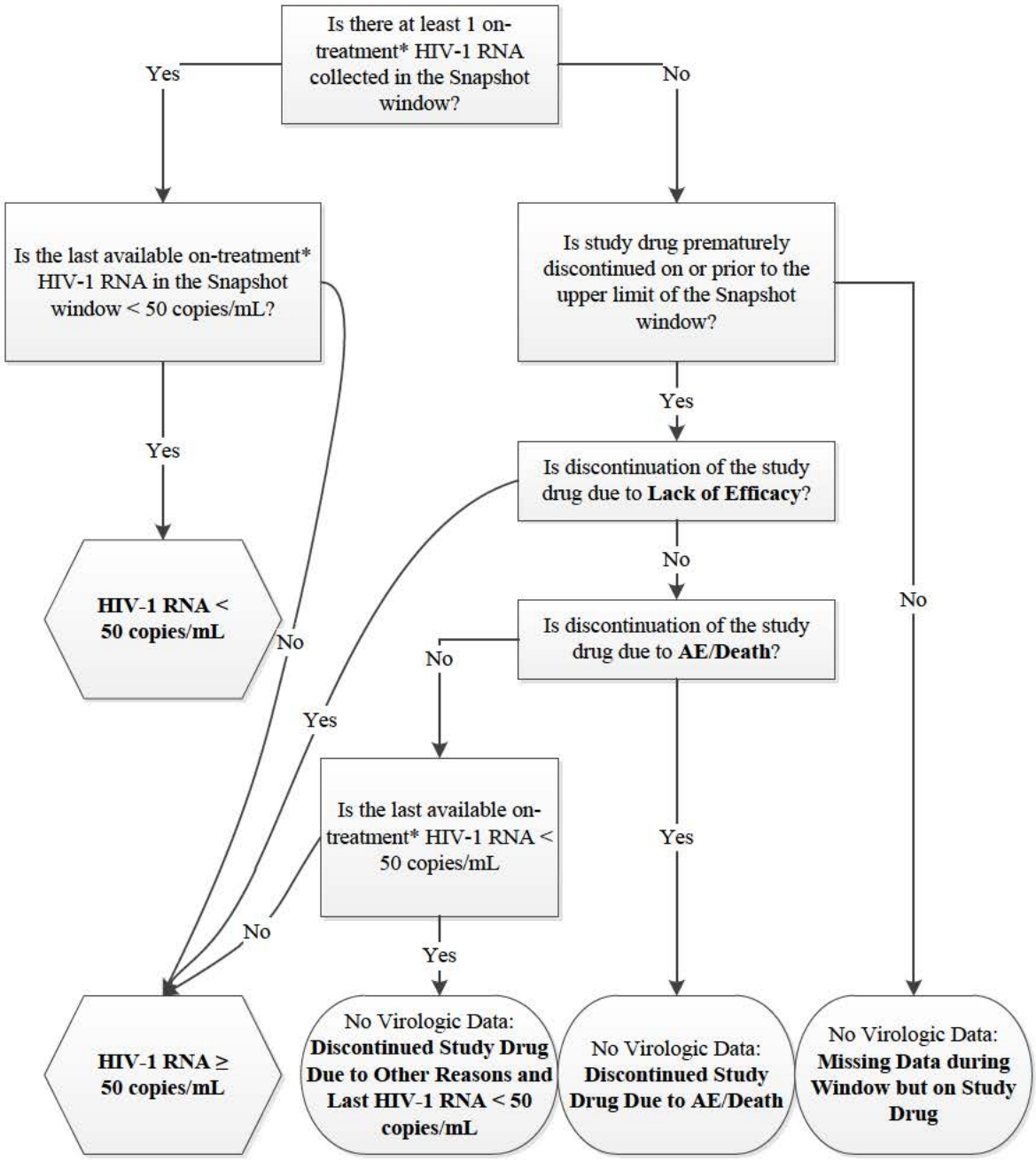
a Once the last participant completes the Week 96 visit and Gilead completes the Week 96 analysis, all participants will return to the clinic (within 30 days ± 6 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC is demonstrated for the HIV-1 and HBV coinfected participants following review of unblinded data, participants 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 extension phase until the product becomes accessible to participants through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

b Open label study drug, B/F/TAF FDC will be dispensed to participants participating in the Open-Label Rollover extension.

c Participants who discontinue study drug during the open label rollover extension portion of the study 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 participant will not continue attending the scheduled study visits.
d Symptom-directed physical examination as needed.
e HIV-1 genotype and phenotype testing for participants with virologic failure. Following virologic rebound, participants 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 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.14).
f Any adverse event 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 Day 1, or is otherwise explained.
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × ULN). At End of Blinded Treatment Visit and every 24 weeks after the End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
i 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) every 24 weeks. If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j Complete blood count with differential and platelet count.
k Participants who complete the open-label rollover extension will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit. Participants who permanently discontinue study drugs during the open-label rollover extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit 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.
l Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the End of Blinded Treatment Visit date through Week 12 OL and completed within ± 6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified.
m HBV serology (HBsAg and reflex anti-HBs Ab, and HBeAg and reflex anti-HBe Ab will be performed every 48 weeks.
n Hepatitis C virus (HCVAb) serology will be performed every 48 weeks. Participants who are HCVAb positive will have a HCV RNA test performed.
o Plasma and serum blood storage samples will be collected for safety, virology or PK testing.

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Naïve 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 data include all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug.

Appendix 3. Region Definition

Region	Country Name	Number of Participants in Safety Analysis Set (N=243)
Asia	China (CHN)	56
	Hong Kong (HKG)	5
	Japan (JPN)	7
	Korea (KOR)	2
	Malaysia (MYS)	37
	Thailand (THA)	94
	Taiwan (TWN)	12
Other	Dominican Republic (DOM)	10
	Spain (ESP)	7
	Turkey (TUR)	9
	United States (USA)	4

Appendix 4. Adverse Events of COVID-19

An adverse event record will be flagged as adverse events for COVID-19 if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following COVID-19 SMQs under MedDRA version 24.1 provided by Gilead PS (search name: COVID-19 (SMQ) – Narrow) and reviewed by Gilead medical monitors.

	SMQ Source
AEs for COVID-19	COVID-19 (SMQ) (Narrow Scope)

Appendix 5. Data Collection of COVID-19 Data

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

Data Collection

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

Determination of Missed and Virtual Visits

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

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

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

iii. Otherwise result is missing

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

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

Appendix 6. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA version 25.1 provided by Gilead PS (search name: Non-infectious, non-congenital hepatobiliary disorders) and reviewed by Gilead medical monitors.

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

Appendix 7. 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),

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

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

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

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

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

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

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

4. Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the participant is randomized (ie, participant with nonmissing 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 participant took at least 1 dose of study drug and assigned as blank if participant never dosed.

6. Enrollment by Stratum: using actual HBeAg, HBV DNA and CD4+ cell count screening value, the last screening value (with visitnum < 0) prior to randomization date and time.

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

8. For the definition of Full Analysis Set regarding (3) have at least 1 post baseline HIV-1 RNA or HBV DNA results while on study drug: on study drug means the same as on-treatment (ie, postbaseline data up to 1 day after permanent discontinuation of study drug or all available postbaseline data for participants who were still on study drug).

9. Body mass index (BMI)

BMI will be calculated as follows:

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

Baseline height and weights measured at each visit will be used for this calculation.

10. Please note, “Not Permitted”, “Unknown”, or missing categories will be excluded for percentage calculation. For Mode of infection (HIV and HBV Risk Factors), where “Unknown” will be included for percentage calculation, since a participant may fit more than 1 HIV risk factors, percentage may add to more than 100%.

11. Last Dose Date and Last Study Date

    a) Last Dose Date (ie, TR01EDT or TR01EDTC for randomized phase last dose date, and TR02EDT or TR02EDTC for extension phase last dose date) in ADSL was defined in Section 3.8.1.

Randomized Phase Last Dose Date:

For **B/F/TAF** or **DTG + F/TDF** subjects with a partial last dosing date (ie, month and year of last dose are known), the minimum of {(extension phase first dose date – 1 day, if available), (the latest of the dispensing dates of study drug bottles, study drug start dates and end dates (based on EX dataset with study drug in randomized phase), 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.

Extension Phase Last Dose Date:

For subjects with a partial last dosing date (ie, month and year of last dose are known), the minimum of { (the latest of the dispensing dates of study drug bottles, study drug start dates and end dates (based on EX dataset with study drug in extension phase), 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 study date, the complete death date should be used as the imputed last study date.

b) Last Study Date is the latest of the randomized or extension phase (if available) study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date. If study drug start dates 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 participant 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. Toxicity Grades:

Two type of treatment emergent lab abnormalities flag variables will be derived for laboratory data as applicable. For treatment emergent flag used in listing for randomized analysis set, the baseline toxicity grade will be based on baseline value defined as the last nonmissing value obtained on or prior to the first dose of randomized study drug. For treatment emergent flag used for the All B/F/TAF analysis summary and listing using all B/F/TAF analysis set, the baseline toxicity grade will be based on baseline value defined as the last nonmissing value obtained on or prior to the first dose of B/F/TAF.

Treatment-emergent laboratory abnormalities will be summarized for all B/F/TAF analysis, following the same rule bellows.

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

b) For glucose grading, as specified in this program specification Section 7.2, 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.

13. TEAE

Events with Missing Onset Day and/or Month

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

a) 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

b) 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

c) End date is as follows:

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

   ii) 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

   iii) 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.

14. Graded Laboratory Abnormalities Summary

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	N/A
	Prothrombin Time (PT)	Increase	N/A
Urinalysis	Urine Blood	Increase	N/A
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative)

Note: Prothrombin Intl. Normalized Ratio (INR) and Prothrombin Time (PT) were graded based on the protocol defined toxicity grade scale. The results and toxicity grade will be listed in listing, but not be summarized in lab toxicity summary table.

15. Concomitant nonstudy-drug ARV medications (for all B/F/TAF analysis (ie, ARV medications other than study drug that are taken while receiving study drug B/F/TAF) 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 7.5)

16. Lipid modifying medication analyses for All B/F/TAF analysis:

Lipid modifying medication is defined to be the concomitant medication with ATC2 term = "LIPID MODIFYING AGENTS" and CMDECOD contains wording of "STATIN" in the ADCM dataset.

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).

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 before first dose of B/F/TAF (including both phases), they will NOT be considered initiated lipid modifications while receiving B/F/TAF for the all B/F/TAF analysis.

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).

17. 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.

18. HIV/HBV/HCV Coinfection:

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

Label	LBTESTCD	LBTEST	Possible Values
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**

- For baseline coinfection, for all B/F/TAF analysis, the baseline would be adjusted based on the first dose of B/F/TAF (including both phases), when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date of B/F/TAF (including both phases)for each test (eg, HBcAb)

  — 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

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 participant is considered to have incident coinfection

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

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

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

* Participants with positive HCVAb postbaseline must also have negative or missing HCVAb at baseline in order to be considered as having incident HIV/HBV/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 of B/F/TAF (including both phases) and on or prior to the last dose date

  — 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".

19. HBV DNA test codes: If the result of the lab 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.

The new Cobas 6800 Assay for HBV DNA can be identified based on SDTM.LB.LBCAT='GENOMICS'.

20. The TEAE definitions will be applied to the double-blind randomized phase data and the OL extension phase data, separately. When randomized phase data are used, AEs onset date will be compared with the randomized phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the randomized phase. An AE meeting the TEAE criteria will be considered as a TEAE in the randomized phase. When OL extension phase data are used, AEs onset date will be compared with the extension phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the extension phase. AE meeting the TEAE criteria will be considered as a TEAE in the OL extension phase.

One AE will be included either in the double-blind randomized phase or OL extension phase, but not both, except that an AE is treatment-emergent in the randomized phase, but continuing into extension phase and leading to prematurely discontinuation of the study drug in the extension phase, which will be counted as treatment-emergent for both phases. When an AE with missing onset date and according to the following rules for incomplete dates, an AE is treatment emergent in the OL extension phase, then the AE will be included in OL extension phase and considered treatment emergent in OL extension phase only.

Events with Missing Onset Day and/or Month

An AE 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.

SAP-Final-GS-US-380-4458

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Global Development Lead (GDL) eSigned	10-Apr-2024 00:34:58
PPD	Biostatistics eSigned	10-Apr-2024 14:18:07