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)
Study Number:	GS-US-380-4458
Protocol Version (Date):	Amendment 2 (06 July 2018)
Analysis Type:	Week 48 Interim Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	31 March 2022
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
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 Week 48 interim analysis for Study GS-US-380-4458, which will be performed when all subjects have completed their Week 48 visit 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 a 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 subjects 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 subjects as determined by the proportion of subjects 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 subjects 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 subjects 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 subjects 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 Subject Population

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

Treatment Groups

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

- **Treatment Group 1 (n=120):** FDC of BIC 50 mg/FTC 200 mg/ TAF 25 mg + placebo to match DTG 50 mg and placebo to match FDC of FTC 200 mg/TDF fumarate 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

Subjects 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 naive with plasma HIV-1 RNA ≥ 500 copies/mL at Screening
  2) ≤ 10 days of prior therapy with any antiretroviral agent, including lamivudine, entecavir and approved or experimental integrase inhibitors following a diagnosis of HIV-1 infection (except the use for pre-exposure prophylaxis [PrEP] or post-exposure prophylaxis [PEP], up to one month prior to screening)
  3) Screening HIV-1 genotype report must show sensitivity to FTC and TFV (tenofovir).
- 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 subjects will be treated for at least 96 weeks during the blinded treatment phase. Following the Screening and Day 1 visits, subjects will be required to return for study visits at Weeks 4, 8, 12 and every 12 weeks thereafter.

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

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

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

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

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 96 weeks. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks from Week 12 though Week 96. After Week 96, all subjects will continue to take their blinded study drugs and attend 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 subjects (HBV DNA > 69 IU/mL) at Weeks 48, 96 or early study drug discontinuation as early as Week 8, as well as all subjects who meet virologic breakthrough criteria.

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

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

Pharmacokinetics

Trough pharmacokinetics (PK) blood sample will be obtained 20-28 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 post-dose at Weeks 8 and 24.

Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 Treatment Groups (Treatment Group 1: Treatment Group 2). Randomization will be stratified by 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 and HBV naïve, HIV-1 and HBV co-infected subjects, randomized in a 1:1 ratio to 2 treatment groups (120 subjects 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 subjects also provides 81% power to detect a non-inferiority margin of 12% with respect to the co-primary efficacy endpoint of the proportion of subjects 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 will be conducted after all subjects enrolled have completed their Week 24 visit or prematurely discontinued from the study drug. The purpose of this interim analysis is to provide the IDMC with a statistical report for review. More details are documented in the IDMC charter.

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

2.2. Interim Analyses

2.2.1. Week 48 Analysis

The Week 48 analysis will be conducted after all subjects either complete their Week 48 visit or prematurely discontinue from the study drug.

This statistical analysis plan describes the analysis plan for the Week 48 interim analysis, the primary analysis of this study.

2.2.2. Week 96 Analysis

The Week 96 analysis will be conducted after all subjects either complete their Week 96 visit or prematurely discontinue from the study drug.

2.3. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

By-subject listings will be presented for all subjects in the All Randomized Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

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

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before 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 subjects 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 subjects who are randomized into the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug, (3) have at least 1 post baseline HIV-1 RNA or HBV DNA results while on study drug. Subjects will be grouped according to the treatment to which they were randomized. For the FAS, all efficacy data, including data collected after the last dose of study drug, will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set for HIV Efficacy Analysis

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

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

- Subjects who do not have on-treatment HIV-1 RNA in the Week 48 analysis window, except when missing due to discontinuation of study drug for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation in the "Blinded Treatment" study phase on the study drug completion eCRF page; Table 3-1).

Table 3-1. Subjects Excluded from Week 48 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window

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

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

- Subjects who do not meet the inclusion criterion that the screening genotype report must show sensitivity to FTC and TFV.
- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in Protocol Section 4.3 including drugs not to be used with BIC, FTC, DTG, TAF, and TDF.
- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 48 Visit below the 2.5th percentile.

3.1.4. Per Protocol Analysis Set for HBV Efficacy Analysis

The Week 48 **PP Analysis Set for HBV Efficacy Analysis** is defined in a similar way to the week 48 PP analysis set for HIV efficacy analysis, except that HIV-1 RNA will be replaced with HBV DNA as the evaluation criterion, will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received.

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

- Subjects who do not have on-treatment HBV DNA in the Week 48 analysis window, except when missing due to discontinuation of study drug for lack of efficacy.
- Subjects who do not meet the inclusion criterion that the screening genotype report must show sensitivity to FTC and TFV.

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in Protocol Section 4.3 including drugs not to be used with BIC, FTC, DTG, TAF, and TDF.

- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 48 Visit below the 2.5th percentile.

3.1.5. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug. All the data collected up to 30 days after permanent discontinuation of the study drug will be included in the safety summaries, unless specified otherwise. Subjects will be grouped according to the treatment they actually received. This is the primary analysis set for safety analyses.

3.1.6. Serologically Evaluable Full Analysis Set

3.1.6.1. Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion

The Serologically Evaluable Full Analysis Set for HBsAg loss/seroconversion includes all subjects who were in the Full Analysis Set, and with HBsAg positive and HBsAb negative or missing at baseline. Subjects will be analyzed according to the treatment they were randomized to.

3.1.6.2. Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion

The Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion includes all subjects who were in the Full Analysis Set, and with HBeAg positive and HBeAb negative or missing at baseline. Subjects will be analyzed according to the treatment they were randomized to.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS, subjects will be grouped by randomized treatment. For other analyses, subjects will be grouped by actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

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.

HIV efficacy analyses will include 2-level HIV-1 RNA stratum ($\leq$ 100,000 vs. $>$ 100,000 copies/mL) at baseline as stratification factor. Based on pervious HIV studies, we knew that baseline CD4 cell count had more pronounced impact on the snapshot outcome than baseline HIV-1 RNA, and baseline CD4+ cell count are highly correlated with HIV-1 RNA. As a

result, we chose CD4 cell count as one of the 3 stratification factors at randomization to avoid having too many stratification factors. Since baseline CD4 cell count is included as one of the stratification factors, it is expected to have a balanced distribution between the two treatments, and therefore it is not necessary to include baseline CD4 cell count as a stratification factor for HIV efficacy analysis. Instead, we include baseline HIV-1 RNA as a stratification factor for HIV efficacy analysis.

HBV efficacy analyses will include baseline HBeAg status (positive vs negative) and baseline HBV NDA level (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL) as stratification factors.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} and the proportion of subjects with HBV DNA < 29 IU/mL will be analyzed for the following subject subgroups (see Section 4 for details):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) Male and (b) Female
- Region: (a) Asia and (b) Other
- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 48 visit)
- Race: (a) Asian and (b) Non-Asian
- Baseline HIV-1 RNA level (copies/mL): (a) ≤ 100,000 and (b) > 100,000 for HIV efficacy endpoint only
- Baseline CD4+ cell count (/μL): (a) < 200 and (b) ≥ 200 for HIV efficacy endpoint only
- Baseline HBeAg: (a) Positive and (b) Negative for HBV efficacy endpoint only
- Baseline HBV DNA level (IU/mL): (a) < 8 $\log_{10}$ and (b) ≥ 8 $\log_{10}$ for HBV efficacy endpoint only
- HBV Genotype: (a) A/D, (b) B/C, and (c) Other for HBV efficacy endpoint only
- Baseline ALT by central laboratory normal range: (a) ≤ upper limit of normal (ULN) and (b) > ULN for HBV efficacy endpoint only

3.4.2. Subject Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs will be analyzed for the following subject subgroups (also see Section 7.8):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) Male and (b) Female
- Race: (a) Asian and (b) Non-Asian
- Region: (a) Asia and (b) Other
- Baseline HIV-1 RNA level (copies/mL): (a) ≤ 100,000 and (b) > 100,000
- Baseline CD4+ cell count (/μL): (a) < 200 and (b) ≥ 200
- Baseline HBeAg: (a) Positive and (b) Negative
- Baseline HBV DNA level (IU/mL): (a) < 8 $\log_{10}$ and (b) ≥ 8 $\log_{10}$
- HBV Genotype: (a) A/D, (b) B/C, and (c) Other
- Baseline ALT by central laboratory normal range: (a) ≤ ULN and (b) > ULN

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

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

3.5. Multiple Comparisons

The noninferiority evaluations of the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm and the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 by Missing = Failure (M=F) approach are the prespecified primary comparisons. However, 1 interim IDMC analysis will be performed prior to the analysis for the primary endpoints and an alpha penalty of 0.00001 will be applied for this interim IDMC meeting. Therefore, the alpha level for the primary endpoints is adjusted to 0.04999 (corresponding to 95.001% confidence interval [CI]) using both the FAS and the Week 48 PP analysis set.

To control type I error for the assessment of the primary and the co-primary efficacy endpoints at Week 48, the hypothesis testing will be performed using the fixed sequence-testing procedure {Maurer 1995} in the sequential order with pre-specified 1-sided alpha level. (detail see Section 6.1.2.3).

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

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

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for concomitant 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 subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject 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.

Natural logarithmic transformations will be used for analyzing concentrations in plasma PK samples. Concentration values (including trough and single postdose PK concentration) that are below the lower limit of quantitation (BLQ) will be presented as "BLQ" in the concentration listing, and will be treated as one-half the value of the lower limit of quantitation at postdose time points for summary purposes.

If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.8. Analysis Windows

3.8.1. Definition of Study Day

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

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

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

If last dose date is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued or completed blinded study drug at the data cut date, the latest of the study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, 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.

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

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments, unless specified otherwise.

3.8.2. Analysis Windows

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

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 3-2.

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

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

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.

Table 3-3. Analysis Windows for HBV Serology

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

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 3-4.

Table 3-4. Analysis Windows for Metabolic Assessments

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

The analysis windows for renal function (including urine RBP and urine beta-1-microglobulin) are presented in Table 3-5.

Table 3-5. Analysis Windows for Renal Function

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 3-6.

Table 3-6. Analysis Windows for HCV Serology and HCV RNA

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

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, 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 (eg, abnormal will be selected over normal for safety ECG findings).
- 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.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects randomized at each region, country, and investigator will be summarized by treatment group and overall using the safety analysis set. The denominator for this calculation will be the number of subjects in the safety analysis set. Similarly, the number and percentage of subjects enrolled in each randomization stratum will be summarized based on reclassified strata using screening HBeAg (positive or negative), HBV DNA, and CD4+ Cell Count data instead of using interactive web response system (IWRS) data.

If there are discrepancies between IWRS and laboratory data with regard to stratum assignment, a listing of the discrepancies will be provided. If there are differences between randomization stratum using screening value and baseline value, a listing of the differences will be provided.

4.1.2. Subject Disposition

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

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

- Still on study drug up to the data cut date
- Prematurely discontinuing study drug prior to the data cut date (with summary of reasons for discontinuing study drug)
- Still on study up to the data cut date
- Prematurely discontinuing from study prior to the data cut date (with summary of reasons for discontinuing study)

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

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 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). For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date.

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

Summaries will be provided by treatment group for subjects in the safety analysis set. No inferential statistics will be provided.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group based on the safety analysis set. The log rank test will be used to compare the difference in study drug exposure between the 2 treatment groups. Subjects who are still on the randomized study drug will be censored on the imputed last dose date as defined in this section. A plot of KM estimates for the time to premature discontinuation of study drug by treatment group will be generated.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts for active drug only (eg, study drug regimen in Treatment Group 1 includes 1 study drug: *B/F/TAF active*. Study drug regimen in Treatment Group 2 includes 2 study drugs: *DTG active + F/TDF active*). 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.

Adherence up to the data cut date will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or using all data available for subjects who are ongoing on study drug.

Adherence up to Week 48 visit will also be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or the Week 48 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for adherence up to the data cut date and adherence up to Week 48 visit for a study drug regimen (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for subjects who return at least 1 bottle and have calculable adherence during the study in the safety analysis set. No inferential statistics will be provided.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the Full Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation. A listing of subjects 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 has an impact on the study conduct. Some subjects 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.

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

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

4.4.3. Missed and Virtual Visits due to COVID-19

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

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex at birth, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The summaries of demographic data and baseline subject characteristics will be provided for the safety analysis set.

For categorical demographic and baseline characteristics, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups. For continuous demographic and baseline characteristics, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

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:

- 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:

- 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}, (b) Negative and >= 8 log_{10}, (c) Positive and < 8 log_{10}, and (d) Negative and < 8 log_{10}
- 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 subject was first documented to be HBV positive)

For categorical baseline disease characteristics, the CMH test (general association statistic for nominal data, and row means scores differ statistic for ordinal data) will be used to compare the 2 treatment groups. For continuous baseline disease characteristics, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

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

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoints

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

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

6.1.1.1. US FDA-defined Snapshot Algorithm

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

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

b) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,

c) Missing data during the window but on study drug.

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

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

6.1.1.2. Missing = Failure Approach for Primary HBV Efficacy Endpoint

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 subjects who were still on study drug) for subjects in the FAS. The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 will be analyzed using a Missing = Failure approach. In this approach, all missing on-treatment data will be treated as HBV DNA ≥ 29 IU/mL

- **HBV DNA < 29 IU/mL:** this includes subjects who have on-treatment HBV DNA < 29 IU/mL in the Week 48 analysis window

- **HBV DNA ≥ 29 IU /mL, this** includes subjects

  a) Who have on-treatment HBV DNA ≥ 29 IU/mL in the Week 48 analysis window, or

  b) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or

  c) Who discontinue study drug prior to or in the Week 48 analysis window due to adverse event (AE) or death, or

  d) Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than adverse event (AE), death, or lack of efficacy, or

  e) Who is still on study drug but missing on-treatment HBV DNA data during the Week 48 analysis window.

6.1.2. Primary Analyses of the Primary Efficacy Endpoints

6.1.2.1. Analysis of HIV Primary Efficacy Endpoint

The null hypothesis is that the proportion of subjects achieving HIV-1 RNA < 50 copies/mL (as defined by the US FDA-defined snapshot algorithm) at Week 48 in B/F/TAF is at least 12% lower than the response rate in DTG + F/TDF; the alternative hypothesis is that the response rate in B/F/TAF is less than 12% lower than that in DTG + F/TDF.

The analysis purpose of the primary efficacy endpoint is to assess the noninferiority of treatment with B/F/TAF relative to treatment with DTG + F/TDF. Noninferiority will be assessed using a conventional CI approach, with a noninferiority margin of 12%.

For the interim analysis for Week 24 IDMC, an alpha of 0.00001 will be spent. Therefore, the significance level for the 2-sided test in the primary analyses at Week 48 will be 0.04999 (corresponding to 95.001% CI).

The baseline stratum weighted treatment difference (B/F/TAF – DTG+F/TDF) and the associated 2-sided 95.001% CI will be constructed using a normal approximation method based on stratified Mantel-Haenszel (MH) proportions as described as follows {Koch 1989}, where stratification factor include baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL):

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} * SE(P_1 - P_2),$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{1h} - p_{2h}$ is the difference in the response rate between of the Treatment Groups 1 and 2 in stratum h (h = 1 to 2).
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of the Treatment Groups 1 and 2 in stratum h.
- $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 \left[\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1} \right]}{(\sum w_h)^2}}$, where $p_{1h}^* = \frac{m_{1h}+0.5}{n_{1h}+1}$ and $p_{2h}^* = \frac{m_{2h}+0.5}{n_{2h}+1}$. m_{1h} and m_{2h} are the number of subjects with HIV-1 RNA < 50 copies/mL in the Treatment Groups 1 and 2 in stratum h.
- $\alpha = 0.04999$ for this study.
- $Z_{(1-\alpha/2)} = Z_{0.975005} = 1.96005$ is the 97.5005th percentile of the normal distribution.

Note that if the computed lower confidence bound is less than –1, the lower bound is defined as –1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL , HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 48 will be summarized.

It will be concluded that B/F/TAF is noninferior to DTG + F/TDF if the lower bound of the 2-sided 95.001% CI of the difference (B/F/TAF – DTG+F/TDF) in the response rate is greater than -12%.

If noninferiority of B/F/TAF to DTG+F/TDF is established, the same 95.001% CI used in evaluating noninferiority at Week 48 will be used to evaluate superiority. If the lower bound of the 95.001% CI is greater than 0, then superiority of B/F/TAF to DTB+F/TDF is established. The stratified 2-sided CMH test will also be used to assess superiority as a secondary assessment, where baseline stratum include baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL). The FAS will be used for this primary efficacy endpoint analysis and the superiority evaluation.

6.1.2.2. Analysis of Co-Primacy HBV Efficacy Endpoint

The null hypothesis is that the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 as determined by Missing = Failure approach in B/F/TAF is at least 12% lower than the response rate in DTG + F/TDF; the alternative hypothesis is that the response rate in B/F/TAF is less than 12% lower than that in DTG + F/TDF. For missing = Failure approach, all missing data will be treated as HBV DNA ≥ 29 IU/mL.

The number and percentage of subjects who achieved and did not achieve HBV DNA < 29 IU/mL, and reasons for no HBV DNA data at Week 48 will be summarized.

Noninferiority will be assessed similarly as for the HIV primary efficacy endpoint, except the stratification factors include baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL). If the number of subjects in a particular stratum is too small, this stratum may be combined with other strata for analysis.

It will be concluded that B/F/TAF is noninferior to DTG + F/TDF if the lower bound of the 2-sided 95.001% CI of the difference (B/F/TAF – DTG+F/TDF) in the response rate is greater than -12%.

If noninferiority of B/F/TAF to DTG+F/TDF is established, the same 95.001% CI used in evaluating noninferiority at Week 48 will be used to evaluate superiority. If the lower bound of the 95.001% CI is greater than 0, then superiority of B/F/TAF to DTB+F/TDF is established. The stratified 2-sided CMH test will also be used to assess superiority as a secondary assessment, where baseline stratum include baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL).

The FAS will be used for the above primary efficacy endpoint analyses and the superiority evaluations.

For the Missing = Failure approach for HBV DNA, the number and percentage of subjects with HBV DNA in the following categories will also be summarized by treatment group for all visits up to Week 48:

- < 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
- Missing

The proportion of subjects with HBV DNA < 29 IU/mL by Missing = Failure approach at each postbaseline visit will be analyzed using the same statistical method applied to the primary analysis of the primary efficacy endpoints. In addition, the 95% CI of the proportion of subjects with HBV DNA < 29 IU/mL within each treatment will be provided using the Clopper-Pearson Exact method.

For the Missing = Failure approach, the proportion of subjects with HBV DNA < 29 IU/mL will be plotted by treatment group for all visits up to Week 48.

6.1.2.3. Analysis of Primacy Efficacy Endpoints using the Fixed Sequence-Testing Procedure

To control type I error for the assessment of the primary and the co-primary efficacy endpoints, the hypothesis testing will be performed using the fixed sequence-testing procedure {Maurer 1995} in the sequential order with pre-specified 1-sided alpha level. The primary hypothesis of noninferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the FDA snapshot analysis) will be tested first. Non-inferiority test will be performed at 1-sided, 0.024995 alpha level. If non-inferiority is established, the co-primary hypothesis of non-inferiority of B/F/TAF relative to DTG + F/TDF, with respect to the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 will be tested second at 1-sided, 0.024995 alpha level. Otherwise, the co-primary endpoint will not be tested at all.

6.1.3. Secondary Analyses of the Primary Efficacy Endpoints

Secondary analyses based on the Week 48 PP analysis sets will be performed to evaluate the robustness of the primary analyses of primary HIV and co-primary HBV efficacy endpoints, respectively. The same adjusted alpha level 0.04999 (corresponding to 95.0001% CI) will be used for these analyses.

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoints

The primacy analyses for the primary HIV and HBV efficacy endpoints described in Section 6.1.2 will be performed within each subgroup specified in Section 3.4.1 based on the FAS, respectively.

For each level of subgroup factors, the difference in proportion between the 2 treatment groups and 95% CIs will be computed based on the MH proportions adjusted by baseline disease characteristics [HIV-1 RNA level (≤ 100,000 copies/mL vs > 100,000 copies/mL) for HIV efficacy endpoint; HBeAg status (positive vs negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL) for HBV efficacy endpoint], if they are not the factors defining the subgroups.

If the sample size in a subgroup is too small, then they will be computed based on normal approximation without stratification.

Additionally, a logistic regression model will be performed which includes the baseline stratification factor(s), subgroup factor, treatment, and treatment by subgroup factor. The baseline stratification factor(s) for HIV efficacy endpoint will include baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL) when analyzing subgroups not defined by the baseline HIV-1 RNA. The baseline stratification factor(s) for HBV efficacy endpoint will include HBeAg status (positive vs negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL) when analyzing subgroups not defined by HBeAg status or the baseline HBV DNA. If a subgroup is defined by the corresponding baseline stratification factor, the logistic regression model will exclude this factor in the model. The odds ratio and the associated 95% CI will be estimated within each subgroup. The homogeneity of the treatment effects between subgroups will be evaluated using a Wald test based on the interaction between treatment and the subgroup factor.

A forest plot of the treatment differences in HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) and HBV DNA < 29 IU/mL (Missing = Failure) at Week 48 and their associated 95% CIs for each subgroup will be generated, respectively.

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 subjects 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

The secondary efficacy endpoints at Week 96 will not be summarized for the Week 48 interim analysis.

6.2.1.2. Secondary HBV Efficacy Endpoints

The secondary HBV efficacy endpoints include:

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

The secondary efficacy endpoints at Week 96 will not be summarized for the Week 48 interim analysis.

For the Week 48 analysis, the following definitions will be used.

- ALT normalization at Week 48 is defined as ALT > ULN (by central laboratory normal range or AASLD normal range) at baseline and ALT ≤ ULN at the given postbaseline visit (ie, Week 48)

- HBsAg loss at Week 48 is defined as HBsAg test result changes from HBsAg positive at baseline to HBsAg negative at the given postbaseline visit (ie, Week 48) with baseline HBsAb negative or missing

Both baseline and postbaseline borderline/equivocal HBV serology results will be imputed using the following rules:

- HBsAg and HBeAg borderline/equivocal will be considered as HBsAg positive and HBeAg positive

- HBsAb and HBeAb borderline/equivocal will be considered as HBsAb negative and HBeAb negative

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

6.2.2. Analysis of the Secondary Efficacy Endpoints

6.2.2.1. Analysis of Secondary HIV Efficacy Endpoints including CD4+ Cell Count and CD4%

The analysis of CD4 cell count will be based on observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) for subjects in the FAS. The changes from baseline in CD4+ cell count and CD4% at Week 48 will be summarized by treatment group using descriptive statistics. The differences in changes from baseline in CD4+ cell count and CD4% between the 2 treatment groups and the associated 95% CI will be constructed using analysis of variance (ANOVA) models, including treatment group (B/F/TAF vs DTG + F/TDF) and baseline HIV-1 RNA (≤ 100,000 vs > 100,000 copies/mL) as fixed effects. The change from baseline in CD4+ cell count and CD4% will also be summarized at visits other than Week 48 by treatment group.

The above analysis of CD4+ cell counts will also be performed using the Week 48 PP analysis set.

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

In addition, the change from baseline in CD4+ cell counts with missing values imputed using the last observation carried forward (LOCF) method will be summarized at each visit (up to week 48 visit in this analysis) based on the FAS. The algorithm for LOCF is as follows:

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) observed before the analysis visit window that has the missing value.

- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no nonmissing postbaseline observation collected prior to that visit.

6.2.2.2. Analysis of Secondary HBV Efficacy Endpoints

The secondary HBV efficacy endpoints in the Week 48 interim analyses include: (1) the proportion of subjects with ALT normalization at Week 48, (2) the proportion of subjects with HBsAg loss at Week 48.

The above 2 HBV efficacy endpoints 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 subjects who were still on study drug) and will be analyzed using both Missing = Failure and Missing = Excluded (M=E) approach. P-values will be calculated using the CMH test stratified by baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 log10 IU/mL vs ≥ 8 log10 IU/mL). The point estimate of the difference in proportions between treatment groups (B/F/TAF – DTG+F/TDF) and the 95% CIs will be constructed using the stratified MH method as described in Section 6.1.2.1 with stratification factors of baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 $\log_{10}$ IU/mL vs ≥ 8 $\log_{10}$ IU/mL), if not the subgroup factor. If the number of subjects in a particular stratum is too small, this stratum may be combined with other strata for analysis.

The proportion of subjects with ALT normalization and the proportion of subjects with HBsAg loss will also be summarized at visits other than Week 48 by treatment group.

The proportion of subjects with ALT normalization at a given visit is defined as the percentage of subjects who had ALT > ULN at baseline and a ALT ≤ ULN at the given post-baseline.

HBsAg loss at a given visit 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.

For the M = F analysis, the proportion of subjects with ALT normalization will be plotted by treatment group for all visits up to Week 48.

The analysis of secondary HBV efficacy endpoints will be based on the FAS.

6.3. Other Efficacy Endpoints

6.3.1. Definition of Other Efficacy Endpoints

The other HIV efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 48 and 96, as defined by 2 different missing data imputation methods specified in Section 6.3.2.1.
- The change from baseline in $\log_{10}$ HIV-1 RNA at Weeks 48 and 96

The other HBV efficacy endpoints include:

- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 as defined by M = E approach

  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 (eg Week 48) is the number of subjects in the FAS with nonmissing HBV DNA value at that visit.
- The proportion of subjects with HBsAg seroconversion to anti-HBs at Weeks 48 and 96

  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 (eg Week 48).
- The proportion of subjects with HBeAg loss at Weeks 48 and 96

  This is defined as HBeAg test result changes from HBeAg positive at baseline to HBeAg negative at a given postbaseline visit (eg Week 48) with baseline HBeAb negative or missing
- The proportion of subjects with HBeAg seroconversion to HBeAb at Weeks 48 and 96

  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 (eg Week 48)
- The change from baseline in $\log_{10}$ HBV DNA (IU/mL) at Weeks 48 and 96

The efficacy endpoints at Week 96 will not be summarized for the Week 48 interim analysis.

6.3.2. Analysis of the Other Efficacy Endpoints

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

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

- Missing = Failure (M = F)

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

- Missing = Excluded (M = E)

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

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

- < 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
- Missing (only applicable for M = F analysis)

The proportion of subjects with HIV-1 RNA < 50 copies/mL as defined by the 2 different missing data imputation methods will be analyzed using the same statistical method applied to the primary analysis of the primary efficacy endpoint. In addition, the 95% CI of the proportion of subjects with HIV-1 RNA < 50 copies/mL within each treatment will be provided using the Clopper-Pearson Exact method.

For the M = F analysis, results will be summarized by treatment group for all visits up to Week 48. For the M = E analysis, results will be summarized by treatment group for all visits through the data cut date.

For the M = F analysis, the proportion of subjects with HIV-1 RNA < 50 copies/mL will be plotted by treatment group for all visits up to Week 48 using the FAS.

6.3.2.2. 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 subjects who were still on study drug) and will be analyzed using both the Missing = Failure and Missing = Excluded methods.

P-value will be calculated using the CMH test stratified by baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 log10 IU/mL vs ≥ 8 log10 IU/mL), if not a subgroup factor. The point estimate of the difference in proportions between treatment groups (B/F/TAF – DTG+F/TDF) and the 95% CIs will be constructed using the stratified MH method as described in Section 6.1.2.1 with stratification factors of baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL), if not a subgroup factor. If the number of subjects in a particular stratum is too small, this stratum may be combined with other strata for analysis.

For the M = F analysis, results will be summarized by treatment group for all visits up to Week 48. For the M = E analysis, results will be summarized by treatment group for all visits through the data cut date.

6.3.2.3. Analyses of the other Efficacy Endpoints involving Change from Baseline

All log_{10} HIV-1 RNA and log_{10} HBV DNA data will be summarized using observed values (ie, missing will be excluded). All log_{10} HBV DNA data 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 subjects who were still on study drug). The change from baseline in log_{10} HIV-1 RNA, log_{10} HBV DNA at Week 48 and other visits will be summarized by treatment group using descriptive statistics based on FAS. The differences in changes from baseline in log_{10} HIV-1 RNA between the 2 treatment groups and the associated 95% CIs will be constructed using ANOVA models, including treatment group (B/F/TAF vs DTG + F/TDF) and baseline HIV-1 RNA level (≤ 100,000 vs > 100,000 copies/mL) as fixed effects. The difference in changes from baseline in log_{10} HBV DNA between the 2 treatment groups and the associate 95% CIs will be constructed using ANOVA models, including treatment group, baseline HBeAg status (positive vs negative), and baseline HBV DNA (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL) as fixed effects.

The mean and 95% CI of change from baseline in log_{10} HIV-1 RNA, log_{10} HBV DNA over time will be plotted using the FAS.

6.4. Changes From Protocol-Specified Efficacy Analyses

The statistical procedure name to assess the primary and the co-primary efficacy endpoints is corrected as fixed sequence-testing procedure {Maurer 1995} from the fallback procedure {Wiens 2005}). Proportion of ALT normalization by visit evaluated using AASLD ULN was also added.

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the safety analysis set. All safety data collected up to 30 days after permanent discontinuation of study drug and all available data for subjects who were still on study drug will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

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 subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the 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 subjects who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

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

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

All treatment-emergent AEs by SOC and PT will be summarized by subgroups defined in Section 3.4.2.

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

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

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnoses (see Protocol Appendix 6). 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 GLPS and reviewed by Gilead medical monitors (see details in Appendix 6).

The number and percentage of subjects with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group based on the safety analysis set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test. 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 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-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

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.

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 subject 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 subject 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 subject 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 subjects 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.

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

Both urine 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 subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects 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 subjects with any nonmissing postbaseline values up to 30 days after last dosing date.

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

7.2.3. Metabolic Laboratory Evaluations

For metabolic assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be estimated from a 2-sided Wilcoxon rank sum test.

In addition, the number and percentage of subjects who took lipid modifying medications at study entry and initiated the medications during the study will be provided, respectively. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test.

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

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

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted 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 subjects who were reported to have the following laboratory test values for postbaseline measurements:

- 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, subjects will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date. Subjects with AST or ALT > 3 × ULN will also be listed.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group and visit using descriptive statistics. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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 days after permanent discontinuation of study drug or the last available date for subjects 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. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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

7.4. 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 up to the date of last dose of study drug will be summarized (number and percentage of subjects) by treatment group and generic name (preferred drug name). Multiple drug use will be counted only once per subject. 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 safety analysis set. Subjects 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-subject listing for ECG assessment results will be provided by subject ID number and visits in chronological order.

7.7. Other Safety Measures

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

7.8. Subject Subgroup for Safety Endpoints

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

7.9. Changes From Protocol-Specified Safety Analyses

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

8. SPECIAL POPULATION ANALYSES

8.1. Analyses for HIV/HBV/HCV Coinfected Subjects

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

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

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

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

The following listings will be provided for subjects with incident HIV/HBV/HCV coinfection while on study drug:

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

9. REFERENCES

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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 subject dosing diary to subjects		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. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Visit even if the subject 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 subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Protocol Section 6.14). Subjects 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. Subjects 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 subjects 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 subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. 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 subjects who complete an End of Blinded Treatment Visit and do not wish to enroll in the open-label rollover extension or those subjects 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 subjects 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 subjects 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. Subjects 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 subject eligibility has been confirmed.

w Genotypic analysis of HBV polymerase/reverse transcriptase (pol/RT) for resistance surveillance will be attempted for all subjects 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)

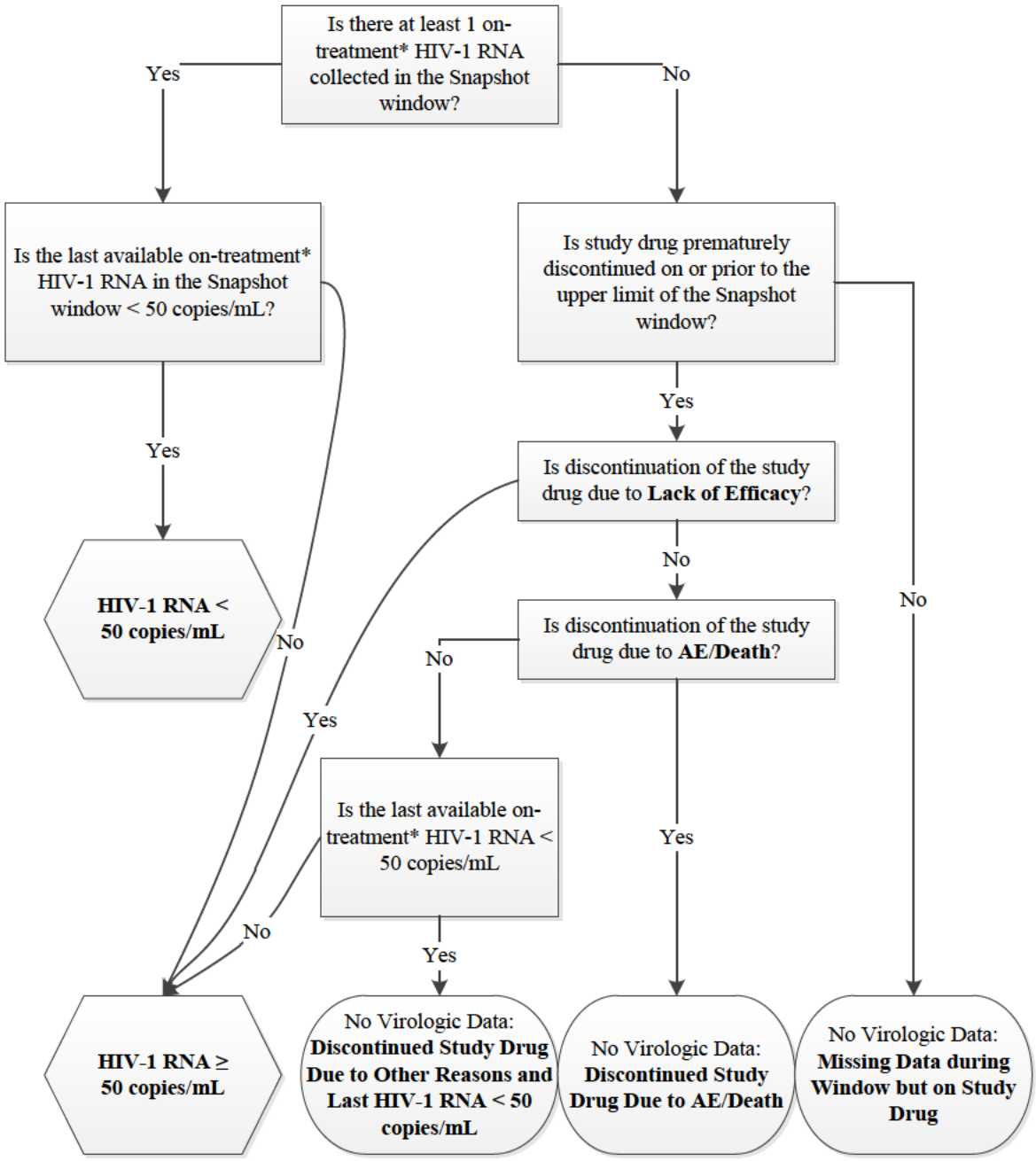
Study Procedures	Post End of Blinded Treatment Visit (every 12 weeks)[a,e,l]	30-Day Follow-up[k]	Early Study Drugs DC[c]
Adverse Events	X	X[f]	X[f]
Concomitant Medications	X	X	X
Complete/Symptom-Directed Physical Exam	X[d]	X[d,f]	**X**[f]
Vital signs (blood pressure, pulse, respiration rate, and temperature) 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 subject completes the Week 96 visit and Gilead completes the Week 96 analysis, all subjects 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 subjects following review of unblinded data, subjects in a country where B/F/TAF FDC is not available, will be given the option to receive B/F/TAF FDC in an open label extension phase until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.

b Open label study drug, B/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension.
c Subjects 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 subject will not continue attending the scheduled study visits.
d Symptom-directed physical examination as needed.
e HIV-1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Protocol Section 6.14).
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 subjects 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 subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j Complete blood count with differential and platelet count.
k Subjects 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. Subjects 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. Subjects 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 Subjects 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 GLPS (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. Determining Missing and Virtual Visits Due to COVID-19

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 X 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 subject and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this subject and this visit will be categorized as "Virtual Visit"

iii. Otherwise result is missing

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

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	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 24.1 provided by Gilead GLPS (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 subjects randomized and never dosed with study drug, age will be calculated from the date of randomization.

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

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

4. Subjects in the randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with 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 subject took at least 1 dose of study drug and assigned as blank if subject 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 subjects 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. SAS codes for the treatment comparison for demographics and baseline characteristics tables.

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

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

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

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

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

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

11. Please note, “Not Permitted”, “Unknown”, or missing categories will be excluded for percentage calculation and also excluded for p value generation for categorical data analysis (eg, CMH test or Fisher exact test). Except for Mode of infection (HIV and HBV Risk Factors), where “Unknown” will be included for percentage calculation, since a subject may fit more than 1 HIV risk factors, therefore percentage may add to more than 100% and no p-value will be generated.

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

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

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

13. Last Dose Date and Last Study Date

    a) Last Dose Date (ie, TRTEDTC, TRTEDT, TR01EDT or TR01EDTC) in ADSL was defined in Section 3.8.1.

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

       If subject died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

       Last dose date is not defined for subjects still on study drug in SAP. However, for the calculation of the duration of exposure to study drug, the data snapshot date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data snapshot date.

    b) Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start 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 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. Last study date is not defined for subjects still on study in SAP. However, for programing purposes, the latest of data snapshot date, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, will be used to impute the last study date for subjects still on study.

14. Toxicity Grades:

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

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

15. Efficacy analyses:

a) For categorical HIV efficacy response (eg, Subjects with HIV-1 RNA < 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between two treatment groups and its 95.001% or 95% CIs are calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) (see SAP Section 6.1.2.1 for details). To test noninferiority, the p-value from 2-sided CMH test (ie, general association test) stratified by baseline HIV-1 RNA stratum should be used, where brnac is the baseline HIV-1 RNA stratum, trtgrp is the treatment, and response is the categorical efficacy response. The following SAS code will be used to compute cell counts and p-value.

```
proc freq data=adeff;
   tables brnac*trtgrp*response/cmh; /*p value from general
   association*/
run;
```

b) For categorical HBV efficacy response (eg, Subjects with HBV DNA < 29 IU/mL as determined by M=F or M=E Analyses): the proportion difference between two treatment groups and its 95.001% or 95% CIs are calculated based on the MH proportion adjusted by baseline HBeAg status (positive vs negative) and baseline HBV DNA (< 8 log10 IU/mL vs ≥ 8 log10 IU/mL) (see SAP Section 6.1.2.2 for details). To test noninferiority, the p-value from 2-sided CMH test (ie, general association test) stratified by baseline HBeAg status and baseline HBV DNA stratum should be used, where bhbeag is the baseline HBeAg status, bdnac is the baseline HBV DNA stratum, trtgrp is the treatment, and response is the categorical efficacy response. The following SAS code will be used to compute cell counts and p-value.

```
proc freq data=adeff;
   tables bhbeag*bdnac*trtgrp*response/cmh; /*p value from general
   association*/
run;
```

c) Subgroup analyses for HIV-1 RNA

i) For the subgroups of age, sex, race, region, baseline CD4+ cell count, and study drug adherence, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HIV-1 RNA stratum** (see Section 6.1.2.1 for details). For example, for the age subgroup, the following SAS code will be used to compute cell counts.

```
proc sort data=adeff;
      by agegrp brnac region;
proc freq data=adeff;
      by agegrp;
      tables brnac*trtgrp*response/cmh;
run;
```

ii) For the baseline HIV-1 RNA subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
      by brnac;
proc freq data=adeff;
      by brnac;
      tables trtgrp*response/ cmh;
run;
```

iii) For the region subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HIV-1 RNA stratum** only. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
      by region brnac;
proc freq data=adeff;
      by region;
      tables brnac*trtgrp*response/ cmh;
run;
```

d) Subgroup analyses for HBV DNA

i) For the subgroups of age, sex, race, region, HBV genotype, baseline ALT and study drug adherence, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HBeAg status and baseline HBV DNA stratum** (see Section 6.1.2.2 for details). For example, for the age subgroup, the following SAS code will be used to compute cell counts.

```
proc sort data=adeff;
      by agegrp bhbeag bdnac;
proc freq data=adeff;
      by agegrp;
      tables bhbeag*bdnac*trtgrp*response/cmh;
run;
```

ii) For the baseline HBeAg subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HBV DNA stratum** only. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
      by bhbeag bdnac;
proc freq data=adeff;
      by bhbeag;
      tables bdnac*trtgrp*response/cmh;
run;
```

iii) For the HBV DNA subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HBeAg status** only. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
      by bdnac bhbeag;
proc freq data=adeff;
      by bdnac;
      tables bhbeag*trtgrp*response/cmh;
run;
```

e) Homogeneity test: Homogeneity Test of Treatment Effect between Subgroups in HIV-1 RNA < 50 copies/mL at Week 48 (Snapshot Algorithm)

i) For the subgroups of age, sex, race, region, baseline CD4+ cell count, and study drug adherence, the odds ratio and the associated 95% CIs are estimated for the response variable (response; coded as 1 for success and 0 for non-success) using a logistic regression model including treatment (trtgrp; coded as 1 for active [ie, B/F/TAF] and 2 for control), baseline HIV-1 RNA stratum (brnac; coded as 1 for < 100,000 copies/mL and 2 for >= 100,000 copies/mL), subgroup factor (coded as 1 for the first subgroup and 2 for the second subgroup), and treatment by subgroup factor. For example, for the age subgroup (agegrp; coded as 1 for < 50 and 2 for >= 50), the following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup:

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

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

ii) For the baseline HIV-1 RNA subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including treatment, subgroup factor, and treatment by subgroup factor. The following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup (the same formats as described in (a) above are assumed):

```
proc genmod data=data descending;
    class trtgrp brnac;
    model response = trtgrp brnac trtgrp* brnac/dist=bin ink=logit
    lrci;
    estimate 'Group 1' trtgrp 1 -1 trtgrp*brnac 1 0 -1 0/exp;
    estimate 'Group 2' trtgrp 1 -1 trtgrp*brnac 0 1 0 -1/exp;
run;
```

iii) Clarification for SE(P1-P2) Calculation in Section 6.1.2.1

- if n_{1h} or $n_{2h} > 1$ the denominator $n_{1h} - 1$ or $n_{2h} - 1$ was calculated as indicated in the formula;
- if n_{1h} or $n_{2h} = 1$, the corresponding n_{1h} or n_{2h} will be adjusted to 2, then corresponding denominator $[(n_{1h} - 1)$ or $(n_{2h} - 1)]$ is 1;
- if n_{1h} or $n_{2h} = 0$ but not both n_{1h} and $n_{2h} = 0$ then not calculable;
- if both n_{1h} and $n_{2h} = 0$ then the corresponding stratum will be ignored, will not be included in the calculation, thus the proportion difference and 95% CI are still calculable.

  If the sample size in a subgroup is too small to calculate the proportion difference between 2 treatment groups and its 95% CI based on the stratum-adjusted MH proportion, then a 95% CI based on the normal approximation will be used. For example, if the stratum-adjusted MH proportion cannot be calculated for sex = “Female” subgroup, the following code will be used to calculate the proportion difference and 95% CI based on the normal approximation, ie, *riskdiff* option in *tables* statement will provide the proportion difference and 95% CI estimations.

```
proc freq data = adeff;
      where sex = "F";
      tables trtgrp*response/ riskdiff(CL=(WALD));
run;
```

f) Homogeneity test: Homogeneity Test of Treatment Effect between Subgroups in HBV DNA < 29 IU/mL at Week 48 (M=F)

i) For the subgroups of age, sex, race, region, HBV genotype, baseline ALT, and study drug adherence, the odds ratio and the associated 95% CIs are estimated for the response variable (response; coded as 1 for success and 0 for non-success) using a logistic regression model including treatment (trtgrp; coded as 1 for active

[ie, B/F/TAF] and 2 for control), baseline HBeAg status, baseline HBV DNA stratum, subgroup factor (coded as 1 for the first subgroup and 2 for the second subgroup), and treatment by subgroup factor. For example, for the age subgroup (agegrp; coded as 1 for < 50 and 2 for >= 50), the following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup:

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

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

ii) For the baseline HBeAg subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including treatment, baseline HBV DNA stratum, subgroup factor, and treatment by subgroup factor. The following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup (the same formats as described in (a) above are assumed):

```
proc genmod data=data descending;
    class trtgrp bhbeag bdnac;
    model response = trtgrp bhbeag bdnac trtgrp* bhbeag/dist=bin
    link=logit lrci;
    estimate 'Group 1' trtgrp 1 -1 trtgrp*bhbeag 1 0 -1 0/exp;
    estimate 'Group 2' trtgrp 1 -1 trtgrp*bhbeag 0 1 0 -1/exp;
run;
```

iii) For the baseline HBV DNA subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including treatment, baseline HBeAg stratum, subgroup factor, and treatment by subgroup factor. The following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup (the same formats as described in (a) above are assumed)::

```
proc genmod data=data descending;
   class trtgrp bhbeag bdnac;
   model response = trtgrp bhbeag bdnac trtgrp*bdnac/dist=bin
   link=logit lrci;
   estimate 'Group 1' trtgrp 1 -1 trtgrp*bdnac 1 0 -1 0/exp;
   estimate 'Group 2' trtgrp 1 -1 trtgrp*bdnac 0 1 0 -1/exp;
run;
```

iv) Clarification for SE(P1-P2) Calculation in Section 6.1.2.1

- if n_{1h} or $n_{2h} > 1$ the denominator $n_{1h} - 1$ or $n_{2h} - 1$ was calculated as indicated in the formula;

- if n_{1h} or n_{2h} =1, the corresponding n_{1h} or n_{2h} will be adjusted to 2, then corresponding denominator [(n_{1h} − 1) or (n_{2h} − 1)] is 1;

- if n_{1h} or n_{2h} = 0 but not both n_{1h} and n_{2h} = 0 then not calculable;

- if both n_{1h} and n_{2h} = 0 then the corresponding stratum will be ignored, will not be included in the calculation, thus the proportion difference and 95% CI are still calculable.

  If the sample size in a subgroup is too small to calculate the proportion difference between 2 treatment groups and its 95% CI based on the stratum-adjusted MH proportion, then a 95% CI based on the normal approximation will be used. For example, if the stratum-adjusted MH proportion cannot be calculated for sex = "Female" subgroup, the following code will be used to calculate the proportion difference and 95% CI based on the normal approximation, ie, *riskdiff* option in *tables* statement will provide the proportion difference and 95% CI estimations.

```
proc freq data = adeff;
      where sex = "F";
      tables trtgrp*response/ riskdiff(CL=(WALD));
run;
```

g) ANOVA model for continuous efficacy variable (eg, CD4+): The differences in changes from baseline in CD4+ cell count between treatment groups and the associated 95% CI will be constructed using an ANOVA, including baseline HIV-1 RNA stratum and treatment as fixed effects in the model.

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

h) Listing for US FDA-defined snapshot outcome:

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

   i) HIV-1 RNA ≥ 50 copies/mL - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL

   ii) No virologic Data - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL

16. 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.

17. Graded Laboratory Abnormalities Summary

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	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.

18. Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.5)

19. Lipid modifying medication analyses:

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

- Subjects who took lipid modifying medications at study entry refer to the subjects who use of the lipid modifying agents at study day 1 (ie, the first dose date). More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in safety analysis set with: 1) any selected CM record with the start date ≤ the first dose date, 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.

- Subjects who initiated lipid modifying medications during the study include the subjects in the safety analysis set who didn't take lipid modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date and on and prior to the last dose date; 2) for subjects who are still on study drug with any selected CM records started after the first dose date.

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

- Lipid modifying medications with the start date prior to the first dose date and the end date completely unknown were considered as being taken at study entry.

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

21) 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, when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date 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 subject 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

* Subjects 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 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".

22) 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.

SAP-Week48-GS-US-380-4458-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Project Team Leader eSigned	01-Apr-2022 16:04:48
PPD	Project Team Leader eSigned	01-Apr-2022 18:33:36
PPD	Biostatistics eSigned	01-Apr-2022 19:14:52