STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Negative, Chronic Hepatitis B
Name of Test Drug:	Tenofovir Alafenamide (TAF)
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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
Anti-HBe	antibody to HBeAg
Anti-HBs	antibody to HBsAg
AST	aspartate aminotransferase (SGOT)
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
bsAP	bone specific alkaline phosphatase
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CHB	chronic hepatitis B
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate
CL_{Cr}	creatinine clearance
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CTX	c-type collagen sequence
CV	coefficient of variation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
FAS	Full Analysis Set
FDA	Food and Drug Administration
$FEPO_4$	fractional excretion of filtered phosphate
FEUA	fractional excretion of uric acid
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
HBeAb	hepatitis B e antibody

HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high density lipoprotein
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low density lipoprotein
LLN	lower limit of the normal range
LLT	lower-level term
LOCF	last observation carried forward
M = E	missing = excluded
M = F	missing = failure
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
OC	osteocalcin
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
pol/RT	polymerase/reverse transcriptase
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
QD	QD
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFFU	Treatment-free Follow-up

TFLs	tables, figures, and listings
TFV	Tenofovir
TFV-DP	tenofovir-diphosphate
TmP	tubular maximum reabsorption rate of phosphate
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WHO	World Health Organization

1. INTRODUCTION

GS-US-320-0108 is a randomized, double-blind, noninferiority study to compare the antiviral activity of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of hepatitis B e antigen (HBeAg)-negative, chronic hepatitis B (CHB) in treatment naive and treatment-experienced participants. For the non-China cohort, 426 participants were planned to be randomized in a 2:1 ratio to receive the blinded treatment for 144 weeks (96 weeks for participants who reached Week 96 prior to consenting for Amendment 3), and were stratified by plasma hepatitis B virus (HBV) DNA level (< 7 log10 IU/mL, ≥ 7 log10 IU/mL < 8 log10 IU/mL, ≥ 8 log10 IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced). All participants who completed the double-blind phase were eligible for participation in the open-label TAF 25 mg extension period for an additional 240 weeks (through Week 384/ED). Participants who already entered the open-label phase at Week 96 per Amendment 1 or 2 and consented to Amendment 3 later were to continue open-label TAF 25 mg QD through Week 384/ED.

Treatment-naive participants are defined as participants with < 12 weeks of previous oral antiviral treatment with any nucleoside or nucleotide analogue. Treatment-experienced participants are defined as participants with ≥ 12 weeks of previous treatment with any nucleoside or nucleotide analogue.

For China, approximately 150 additional participants (100 in TAF group and 50 in TDF group) were planned to be enrolled as agreed upon for local registration purposes. All China cohort participants were to receive the blinded treatment for 144 weeks based on Amendment 3.1, and those who completed the double-blind phase were eligible for participation in the open-label TAF 25 mg extension period for an additional 240 weeks (through Week 384/ED).

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the final clinical study report (CSR) for China (participants enrolled China only). This SAP is based on the study protocol amendment 3.4 dated 25 September 2019 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR for China.

1.1. Study Objectives

The primary and secondary objectives and end points on or before Week 48 were presented in the Week 48 CSR for China. This SAP will focus on the efficacy and safety analyses of all participants after Week 48.

The primary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB at Week 48 in treatment-naive and treatment experienced participants. The primary efficacy parameter is the proportion of participants with plasma HBV DNA levels below 29 IU/mL.

- To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg- negative, CHB at Week 48 in treatment-naive and treatment-experienced participants

The key secondary safety objectives of this study are as follows:

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Week 48

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the change from baseline in serum creatinine at Week 48

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by treatment-emergent proteinuria through Week 48

Other secondary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB in regard to the proportion of participants with plasma HBV DNA levels below 29 IU/mL at Weeks 96 and 144

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB in regard to the proportion of participants with plasma HBV DNA levels below 29 IU/mL (target not detected) at Weeks 48, 96, and 144

- To compare the biochemical (alanine aminotransferase [ALT] normalization) response of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB at Weeks 48, 96, and 144

- To compare the serological response (loss of hepatitis B surface antigen [HBsAg] with seroconversion to anti-HBs) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB at Weeks 48, 96, and 144

- To compare the change in fibrosis as assessed by FibroTest® of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB at Weeks 48, 96, and 144

- To compare the incidence of drug resistant mutations of TAF 25 mg QD versus TDF 300 mg QD at Weeks 48, 96, and 144

- To compare the change from baseline in ophthalmologic findings by fundoscopic examination of TAF 25 mg QD versus TDF 300 mg QDat Weeks 24, 48, 72, 96, and 144 in a subset of participants

- To characterize the pharmacokinetics of TAF and tenofovir (TFV) and determine intracellular concentrations of tenofovir diphosphate (TFV-DP) within peripheral blood mononuclear cells (PBMCs) in participants receiving TAF or TDF

- To evaluate the comparative open-label efficacy, safety and drug resistance mutations of TAF 25 mg QD from Week 144 (Amendment 3.1) through Week 384 in participants initially randomized to TAF 25mg QD and in participants sequentially treated with TDF 300 mg QD for 144 weeks and then switched to open label TAF 25 mg QD

- To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, CHB beyond Week 48 during the double-blind phase in treatment-naive and treatment-experienced participants

1.2. Study Design

1.2.1. Design Configuration and Participant Population

GS-US-320-0108 is a randomized, double-blind, noninferiority study to compare the antiviral activity of TAF 25 mg versus TDF 300 mg for the treatment of HBeAg-negative, CHB in treatment-naive and treatment-experienced participants.

1.2.2. Treatment Groups

Participants were randomized in a 2:1 ratio to the following 2 treatment groups:

- **TAF group:** TAF 25 mg QD + matched placebo of TDF 300 mg QD

- **TDF group:** TDF 300 mg QD + matched placebo of TAF 25 mg QD

For China, approximately 150 additional participants were planned to be randomized in a 2:1 ratio (TAF: TDF) to the treatment groups for local registration purpose.

1.2.3. Key Eligibility Criteria

Participants were to have met the following key eligibility criteria:

- Documented evidence of chronic HBV infection (eg, HBsAg positive for more than 6 months)
- HBeAg-negative, CHB with the following: HBeAg-negative and HBeAb-positive at screening; screening HBV DNA $\geq 2 \times 10^4$ IU/mL; screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and $\leq 10 \times$ ULN (by central laboratory range)
- Estimated creatinine clearance (CL_{Cr}) $\geq$ 50 mL/min (using the Cockcroft-Gault [CG] method) based on serum creatinine and actual body weight as measured at screening

1.2.4. Study Periods/Phases

The duration of randomized, double-blind treatment is 144 weeks (under Amendments 3.1). All participants who complete double-blind phase are eligible for participation in the open-label TAF 25 mg extension period for an additional 240 weeks (through Week 384/ED). All China cohort participants were to receive the blinded treatment for 144 weeks based on Amendment 3.1, and no participant in China entered the open-label phase at Week 96. All participants who complete double-blind period of treatment are eligible for participation in the open-label TAF 25 mg QD extension period. Participants who permanently discontinue study drug (either prematurely [early discontinuation, ED] or at the end of open-label phase [Week 384]) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available HBV therapy, whichever occurs first.

Participants with HBsAg loss, with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs, or after Week 48, if seroconversion occurs prior to this visit. Participants with HBsAg loss with confirmed seroconversion to anti-HBs prior to Week 48 are not permitted to discontinue study drug prior to the Week 48 visit. After Week 48, these participants who discontinue study drug will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 384/ED. Discontinuation of study drug for participants experiencing HBsAg loss with confirmed seroconversion to anti-HBs, who have known bridging fibrosis or cirrhosis, should be considered on a case by case basis.

1.2.5. Schedule of Assessments

Laboratory analyses (serum chemistry, liver tests, hematology, urinalysis, plasma HBV DNA levels, pregnancy testing [for females of childbearing potential]), vital signs, adverse events (AEs), and concomitant medications will be performed at screening, baseline, and every 4 weeks thereafter through Week 48, every 8 weeks through Week 96, every 12 weeks through Week 144, and every 24 weeks through Week 384/ED visit.

HBV serology (HBeAg, reflex hepatitis B e antibody [HBeAb], HBsAg, and reflex hepatitis B surface antibody [HbsAb]) will be performed at screening and baseline, and HBsAg and reflex HBsAb will be performed every 12 to 16 weeks through Week 144, and every 24 weeks through Week 384/ED, and at Follow up Weeks 12 and 24. Quantitative serum HBsAg will be assessed at screening, baseline, every 12-16 weeks until Week 144, every 24 weeks until Week 384/ED, and at all Follow Up visits. Bone and renal biomarker testing will be performed at baseline and then at defined intervals throughout the study. IL28B polymorphism genotype, HBV genotyping and vitamin D assessments will be performed at baseline only. FibroTest® will be performed at baseline, and every 48 weeks thereafter through Week 384/ED. Fasting metabolic assessments (fasting glucose and lipid panel) will be conducted at baseline, every 24 weeks until Week 144, and every 48 weeks until Week 384/ED visit.

Complete physical examinations will be performed at screening, baseline, and Weeks 24, 48, 72, 96, 120, 144, 240, and 384/ED. Symptom directed physical examinations including body weight assessment will be conducted at all other visits. Electrocardiogram (ECG) will be performed at screening and every 48 weeks thereafter.

Only at sites in China with DXA capability, DXA scans of the hip and spine will be conducted during the screening period, and should be conducted at least 14 days prior to the first dose of study drug, and will be subsequently conducted every 24 weeks through Week 144, and every 48 weeks thereafter until Week 384/ ED visit, if not done within the last 24 weeks of ED visit.

Fracture risk assessment will be evaluated at Baseline. In China, this fracture risk assessment will be evaluated at sites with DXA capability only.

Hepatic ultrasound for surveillance of hepatocellular carcinoma will be performed starting at Week 96 and then every 24 weeks thereafter until Week 384/ED. Participants who have completed the Week 96 visit (under Amendment 2.1) should begin ultrasound assessments at the next visit at which an ultrasound assessment is included. Plasma, serum, and urine will be collected at baseline and at every visit thereafter for storage.

Treatment-free Follow-up (TFFU) assessments after premature study drug discontinuation will occur every 4 weeks for 24 weeks and include the following: vital signs, hematology, serum chemistry, liver function tests, and plasma HBV DNA. Plasma, serum and urine will be collected for storage. HBeAg, reflex HBeAb, HBsAg and reflex HBsAb will be evaluated at Follow Up Weeks 12 and 24.

1.2.6. Randomization

Participants will be randomized in a 2:1 ratio to the 2 treatment groups (TAF vs TDF, respectively). Randomization will be stratified by plasma HBV DNA level (< 7 log10 IU/mL, ≥ 7 log10 IU/mL - < 8 log10 IU/mL, ≥ 8 log10 IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced).

1.2.7. Site and/or Stratum Enrollment Limits

Twenty-nine centers participated in China. There was no enrollment limit for individual sites.

1.2.8. Study Duration

The duration of the double-blind treatment is 144 weeks (under Amendment 3.1). After completing the double-blind period of treatment, all participants will be eligible to receive open-label TAF 25 mg once daily, for up to an additional 240 weeks (through Week 384/ED). Participants who permanently discontinue study drug (either prematurely [ED] or at the end of study [Week 384]) will be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available HBV therapy, whichever occurs first.

Participants with HBsAg loss, with confirmed seroconversion to anti-HBs should discontinue study drug within 3 to 6 months following confirmation of seroconversion to anti-HBs or after Week 48, if seroconversion occurs prior to this visit. These participants will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 384/ED.

1.3. Sample Size and Power

For China, approximately 150 additional participants (100 in TAF group and 50 in TDF group) were to be enrolled for local registration purposes.

The sample size and power calculation described below was for non-China participants. With respect to the primary efficacy end point of proportion of participants with plasma HBV DNA levels below 29 IU/mL at Week 48, a sample size of 130 for the TDF group and 260 for the TAF group will have 90% power to rule out the noninferiority margin of 10% at a 1-sided significance level of 0.025. This assumes the expected difference (TAF − TDF) in proportion of participants with HBV DNA < 29 IU/mL is 0 and the proportion of participants with HBV DNA < 29 IU/mL in the TDF group is 91%. A similar response rate in the TDF group was observed in Study GS-US-174-0102.

This sample size (n = 260 for the TAF 25 mg group, n = 130 for the TDF 300 mg group) also provides the following:

- At least 90% power to detect a 1% difference in the percentage change from baseline in hip BMD at Week 48 (assuming a –1.17% change from baseline in TDF 300 mg group and −0.17% change from baseline in the TAF 25 mg group, with a common standard deviation (SD) of 2.20% and a 2-sided $\alpha = 0.025$)

- At least 77% power to detect a 1% difference in the percent change from baseline in spine BMD at Week 48 (assuming a –1.69% change from baseline in the TDF 300 mg group and 0.69% change in the TAF 25 mg group, with a common SD of 3.08% and a 2 sided $\alpha = 0.025$)

- At least 52% power to detect a 0.03 mg/dL difference in the change from baseline in serum creatinine at Week 48 (assuming a 0.04 mg/dL change from baseline in the TDF 300 mg

group and 0.01 mg/dL change from baseline in the TAF 25 mg group, with a common SD of 0.12)

The preceding assumptions were derived from Studies GS-98-437, GS-98-438, GS-US-174-0102, GS-US-174-0103, and GS-US-174-0121.

2. TYPE OF PLANNED ANALYSIS

The final analysis for non-China participants has already been conducted which occurred after the last participant completed the study or prematurely discontinued study. This statistical analysis plan (SAP) describes the analysis plan for the final analysis of participants enrolled in China only.

2.1. Data Monitoring Committee (DMC) Analysis

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant early termination of the study in the best interests of the participants and whether the study should continue as planned or with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC was convened approximately every 24 weeks during the blinded portion of the study and approximately every 48 weeks during the open-label phase. More details are documented in the independent DMC charter. The last DMC meeting was conducted on 24 October 2019 where the DMC members concluded that they would transfer the primary responsibilities for monitoring study conduct and patient safety to Gilead and stand ready to re-engage should concerns arise regarding any aspects of the study.

2.2. Week 48 Analysis (Primary Analysis)

The Week 48 analysis was conducted after the last participant completed the Week 48 visit or prematurely discontinued study drug in China.

2.3. Final Analysis (Week 384)

The final analysis will be conducted after the last participant completes the Week 384 visit or prematurely discontinues study drug in China.

Since no participants entered the TFFU phase after completing the Week 384 visit, this statistical analysis plan (SAP) describes the analysis plan for the Week 384 analysis only and is considered as Final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which participants are included in an analysis. The assignment of participants to analysis sets was done before the study blind was broken for analysis. A summary of the number and percentage of participants in each analysis set will be provided by treatment group and in total.

3.1.1. Randomized Analysis Set

The Randomized Analysis Set includes all participants who were randomized into the study. This is the primary analysis set for by-participant listings.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all randomized participants who have received at least 1 dose of study drug. Participants will be analyzed according to the treatment they actually received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire double-blinded treatment duration.

3.1.3. Open-Label Safety Analysis Set

The Open-Label Safety Analysis Set includes all randomized participants who have received at least 1 dose of open-label study drug. Participants will be analyzed according to the treatment they actually received during the double-blind phase.

3.1.4. Full Analysis Set (FAS)

The FAS includes all randomized participants who have received at least 1 dose of study drug. Participants will be analyzed according to the treatment to which they were randomized.

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

The Serologically Evaluable Full Analysis Set for HBsAg loss/seroconversion includes all participants who were randomized and had received at least 1 dose of study drug, and with HBsAg positive and HBsAb negative or missing at baseline. Participants will be analyzed according to the treatment they were randomized to.

3.1.6. DXA Analysis Set

DXA scans will be performed only at sites in China with DXA capability.

3.1.6.1. Hip DXA Analysis Set

The Hip DXA Analysis Set includes all participants who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline hip BMD values. Participants will be analyzed according to the treatment they actually received.

3.1.6.2. Spine DXA Analysis Set

The Spine DXA Analysis Set includes all participants who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline spine BMD values. Participants will be analyzed according to the treatment they actually received.

3.2. Participant Grouping

Participants will be grouped into the following treatment groups:

Entire study treatment period and double-blind phase summaries:

- Double-blind TAF 25 mg
- Double-blind TDF 300 mg

Open-label phase summaries:

- Double-blind TAF 25 mg participants who switched to open-label TAF 25 mg (TAF-TAF)
- Double-blind TDF 300 mg participants who switched to open-label TAF 25 mg (TDF-TAF)

3.3. Strata and Covariates

Randomization was stratified by plasma HBV DNA level (< 7 log10 IU/mL, ≥ 7 log10 IU/mL - < 8 log10 IU/mL, ≥ 8 log10 IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced) at screening. HBV DNA strata will be reclassified using baseline HBV DNA level for stratified statistical analysis.

3.4. Missing Data and Outliers

3.4.1. Missing Data

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

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

For the primary endpoint and the secondary efficacy endpoints involving proportions, missing data will be handled using M = F approach. Sensitivity analyses will also be performed including M = E approach.

For the remaining endpoints, values for missing data will not be imputed, unless specified otherwise.

3.4.2. Outliers

Outliers will be identified during 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 analysis.

3.5. 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.

Laboratory Data that are continuous in nature but are below the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows except for the scenarios described below for direct bilirubin, urine creatinine, and serum cystatin C:

- A value that is 1 unit less than the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (x is considered as the LOQ). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.

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

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

For direct bilirubin, a value of "< 0.1" is imputed as 0.09. For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios. For serum cystatin C, a value of "< 0.10" is handled as a missing value in the calculation of estimated glomerular filtration rate (eGFR).

Logarithm (base 10) will be used to transform HBV DNA and quantitative HBsAg data.

For HBV DNA, if the value in IU/mL (TaqMan) is above the upper limit of quantification, the corresponding diluted value (TaqDil), if available, will be used.

3.6. Analysis Windows

3.6.1. Definition of Study Day 1 and Other Definitions

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

Open-Label Study Day 1 is defined as the day when the first dose of the open-label study drug was taken, as recorded on the Study Drug Administration eCRF form.

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

Open-Label study days are calculated relative to Open-Label Study Day 1. For events that occurred on or after Open-Label Study Day 1 date, study days are calculated as (visit date − Open-Label Study Day 1 + 1).

Follow-up days are for visits that occur during the 24-week TFFU period and calculated as (visit date – last dose date).

Last Dose Date of Blinded Study Drug is the latest non-missing end date of blinded study drug, recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked for participants who prematurely discontinued blinded study drug or who completed blinded study drug according to Blinded Study Drug Completion eCRF. If the last dose date of blinded study drug is missing (eg, due to lost to follow up) for participants who prematurely discontinued blinded study drug, or for participants who are still on blinded study drug, the latest of nonmissing blinded study drug start dates and end dates, the clinical visit dates and the laboratory visit dates excluding the dates of open-label and 24-week TFFU visits will be used to impute the last dose date of blinded study drug.

For participants who prematurely discontinued blinded study drug or who completed blinded study drug but did not enter open-label phase, the **Last Dose Date** is the same as Last Dose Date of Blinded Study Drug.

For participants who completed blinded study drug and entered open-label phase, the **Last Dose Date** is the latest non-missing end date of open-label study drug, recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked for participants who prematurely discontinued open-label study drug or who completed open-label study drug according to the Open-Label Study Drug Completion eCRF. If the last dose date is missing (eg, due to lost to follow up) for participants who prematurely discontinued open-label study drug, or for participants who are still on open-label study drug, the latest of nonmissing open-label study drug start dates and end dates, the clinical visit dates and the laboratory visit dates excluding the dates of 24-week TFFU visits will be used to impute the last dose date.

Last Study Date is the latest of nonmissing study drug (blinded or open-label) start dates and end dates, the clinic visit and the laboratory visit dates including the 24-week TFFU visit date for participants who prematurely discontinued the study or who completed the study according to Study Completion eCRF.

Baseline value for the double-blind phase (except DXA BMD) is defined as the last nonmissing value obtained on or prior to Study Day 1. For DXA BMD, the baseline value is defined as the last nonmissing value on or prior to Study Day 14. **Baseline value for the open-label phase (except DXA BMD)** is defined as the last nonmissing value obtained on or prior to Open-label Study Day 1. For DXA BMD, it is defined as the last nonmissing value on or prior to Open-Label Study Day 14 and the last dose date of open-label study drug.

3.6.2. Analysis Windows

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

The following windows (shown on Table 3-1 to Table 3-7) apply to baseline and on-treatment assessments only.

For participants who prematurely discontinued the blinded study drug (except participants who discontinue study drug after Week 48 due to HBsAg loss with confirmed seroconversion to anti-HBs during the double-blind phase), laboratory and DXA assessments up to and including the last dose date of the blinded study drug, will be considered as on-treatment during the double-blind phase. For participants who completed the double-blind phase, laboratory assessments up to and including the last dose date of the double-blind study drug + 1 day, and DXA assessments on or prior to the last dose date of the double-blind study drug + 14 days, will be considered as on-treatment during the double-blind phase.

For participants who prematurely discontinued the open-label study drug (except participants who discontinue study drug after Week 48 due to HBsAg loss with confirmed seroconversion to anti-HBs during the open-label phase), laboratory and DXA assessments up to and including the last dose date of the open-label study drug + 3 days, will be considered as on-treatment during the open-label phase. For participants completed the open-label phase, laboratory assessments up to and including the last dose date of the open-label study drug + 3 days, and DXA assessments up to and including the last dose date of the open-label study drug + 14 days, will be considered as on-treatment during the open-label phase. For participants who have not discontinued the open-label study drug permanently, data collected up to database finalization date will be considered as on-treatment of the open-label phase.

For participants who discontinue study drug early due to HBsAg loss with confirmed seroconversion, all efficacy data including data collected after the last dose date of the study drug will be reassigned analysis visits using the on-treatment assessment windows (Table 3-1, Table 3-2, and Table 3-4).

The analysis windows for HBV DNA, hematology, serum chemistry and liver function tests, urinalysis, urine pregnancy test, eGFR (by CG and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), renal biomarkers urine albumin to creatinine ratio (UACR), urine protein to creatinine ratio (UPCR), renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR), urine fractional excretion of filtered phosphate ($FEPO_4$), fractional excretion of uric acid (FEUA), weight, and vital sign assessments are presented in Table 3-1.

Table 3-1. Analysis Windows for HBV DNA, Hematology, Serum Chemistry and Liver Function Tests, Urinalysis, Urine Pregnancy Test, eGFR (by CG and CKD-EPI), UACR, UPCR, TmP/GFR, $FEPO_4$, FEUA, Weight, and Vital Sign Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	125
Week 20	140	126	153
Week 24	168	154	181
Week 28	196	182	209
Week 32	224	210	237
Week 36	252	238	265
Week 40	280	266	293
Week 44	308	294	321
Week 48	336	322	363
Week 56	392	364	419
Week 64	448	420	475
Week 72	504	476	531
Week 80	560	532	587
Week 88	616	588	643
Week 96	672	644	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1091
Week 168	1176	1092	1259
Week 192	1344	1260	1427
Week 216	1512	1428	1595
Week 240	1680	1596	1763
Week 264	1848	1764	1931
Week 288	2016	1932	2099
Week 312	2184	2100	2267
Week 336	2352	2268	2435
Week 360	2520	2436	2603
Week 384	2688	2604	2771

The analysis windows for safety ECG and fibrotest are presented in Table 3-2.

Table 3-2. Analysis Windows for Safety ECG and Fibrotest

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	503
Week 96	672	504	839
Week 144	1008	840	1175
Week 192	1344	1176	1511
Week 240	1680	1512	1847
Week 288	2016	1848	2183
Week 336	2352	2184	2519
Week 384	2688	2520	2855

The analysis windows for BMD results from DXA and fasting lipid panel including direct low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol to HDL ratio, are presented in Table 3-3.

Table 3-3. Analysis Windows for BMD Results from DXA and Fasting Lipid Panel

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1(14[a])
Week 24	168	2(15[a])	251
Week 48	336	252	419
Week 72	504	420	587
Week 96	672	588	839 (755[b])
Week 120[b]	840	756[b]	923[b]
Week 144	1008	840 (924[b])	1175
Week 192	1344	1176	1511
Week 240	1680	1512	1847
Week 288	2016	1848	2183
Week 336	2352	2184	2519
Week 384	2688	2520	2855

a This applies to DXA only. Upper limit for baseline DXA BMD is Day 14 and lower limit for Week 24 DXA BMD is Day 15.
b This applies to the participants who consented to Amendment 3.1.

The analysis windows for serum HBsAg (quantitative) and HBV serology are presented in Table 3-4.

Table 3-4. Analysis Windows for Serum HBsAg (Quantitative) and HBV Serology

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	125
Week 24	168	126	209
Week 36	252	210	293
Week 48	336	294	391
Week 64	448	392	503
Week 80	560	504	615
Week 96	672	616	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1091
Week 168	1176	1092	1259
Week 192	1344	1260	1427
Week 216	1512	1428	1595
Week 240	1680	1596	1763
Week 264	1848	1764	1931
Week 288	2016	1932	2099
Week 312	2184	2100	2267
Week 336	2352	2268	2435
Week 360	2520	2436	2603
Week 384	2688	2604	2771

The analysis windows for fasting glucose, fasting total cholesterol, fasting triglycerides, renal biomarkers including urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and bone biomarkers including C-type collagen sequence (CTX), procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (OC), and bone specific alkaline phosphatase (bsAP) are presented in Table 3-5.

Table 3-5. Analysis Windows for Fasting Glucose, Fasting Total Cholesterol, Fasting Triglycerides, Renal, and Bone Biomarkers

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	55
Week 12	84	56	125
Week 24	168	126	251
Week 48	336	252	419
Week 72	504	420	587
Week 96	672	588	839 (755[a])
Week 120[a]	840	756[a]	923[a]
Week 144	1008	840 (924[a])	1175
Week 192	1344	1176	1511
Week 240	1680	1512	1847
Week 288	2016	1848	2183
Week 336	2352	2184	2519
Week 384	2688	2520	2855

a This applies to the participants who consented to Amendment 3.1.

The analysis window for serum parathyroid hormone (PTH) is presented in Table 3-6.

Table 3-6. Analysis Windows for PTH

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	125
Week 20	140	126	153
Week 24	168	154	181
Week 28	196	182	209
Week 32	224	210	237
Week 36	252	238	265
Week 40	280	266	293
Week 44	308	294	321
Week 48	336	322	363
Week 56	392	364	419
Week 64	448	420	475
Week 72	504	476	531
Week 80	560	532	587
Week 88	616	588	643
Week 96	672	644	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1175
Week 192	1344	1176	1511
Week 240	1680	1512	1847
Week 288	2016	1848	2183
Week 336	2352	2184	2519
Week 384	2688	2520	2855

The analysis window for hepatic ultrasound for hepatocellular carcinoma (HCC) surveillance is presented in Table 3-7.

Table 3-7. Analysis Windows for Hepatic Ultrasound

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 96	672	588	755
Week 120	840	756	923
Week 144	1008	924	1091
Week 168	1176	1092	1259
Week 192	1344	1260	1427
Week 216	1512	1428	1595
Week 240	1680	1596	1763
Week 264	1848	1764	1931
Week 288	2016	1932	2099
Week 312	2184	2100	2267
Week 336	2352	2268	2435
Week 360	2520	2436	2603
Week 384	2688	2604	2855

Hepatic ultrasound data was collected for the participants who consented to Amendment 3.1.

Data collected after the last dose date will be considered as post-treatment visits. Although there's no participant entering TFFU phase after completing Week 384 visit, participants who prematurely discontinued study drug could enter TFFU phase. The analysis windows for post-treatment assessments are presented in Table 3-8 and Table 3-9.

Table 3-8. Analysis Windows for Post-Treatment Assessments Except HBV Serology

Visit ID	Nominal Follow-Up Day	Lower Limit	Upper Limit
Follow-Up Baseline			3
Follow-Up Week 4	28	4	41
Follow-Up Week 8	56	42	69
Follow-Up Week 12	84	70	97
Follow-Up Week 16	112	98	125
Follow-Up Week 20	140	126	153
Follow-Up Week 24	168	154	181

Table 3-9. Analysis Windows for Post-Treatment HBV Serology

Visit ID	Nominal Follow-Up Day	Lower Limit	Upper Limit
Follow-Up Baseline			3
Follow-Up Week 12	84	4	125
Follow-Up Week 24	168	126	209

3.6.3. Selection of Data in the Event of Multiple Records in a 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 1 value per analysis window. When a single value is needed, the following rule(s) will be used.

For baseline of the double-blind and open-label phases, the last available record on or prior to the first dose of blinded and open-label study drug will be selected, respectively. For DXA BMD baseline, the last value on or prior to Study Day 14, and on or prior to Open-Label Study Day 14 and the last dose date of open-label study drug will be selected for the double-blind and the open-label phases, respectively. If there are multiple records with the same time or no time recorded on the same day for numeric observations, an average will be computed for that day, with the exception for HBV DNA and Quantitative HBsAg for which geometric mean will be taken. If there are multiple records with the same time or no time recorded on the same day for categorical observations, the most conservative value will be taken, eg, negative will be selected over positive for HBeAg and HBsAg, and positive will be selected over negative for HBeAb and HBsAb.

The following specified rules will be used for postbaseline visits:

- **ALT:** The largest value will be included in the analysis when 2 or more ALT values occur within the same visit window.
- **BMD:** The latest record in the window will be selected.
- **HBV DNA and Quantitative HBsAg:** 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.
- **Serology:** 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.

For all other laboratory parameters:

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

  — 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 average will be taken.

- If multiple valid nonmissing **categorical** observations (eg, safety ECG results) exist in a window, then records will be chosen as follows:

  — The most conservative value (eg, abnormal will be selected over normal for safety ECG) within the window will be selected. In the event that 2 values within a window are of equal abnormality, the value collected nearest to the nominal date will be used.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment

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

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

4.2. Disposition of Participants

The summary of participant disposition will be provided by treatment group and overall. This summary will include the number of participants in the Randomized Analysis Set, participants randomized but not treated, participants in the Safety Analysis Set, participants in the Open-Label Safety Analysis Set.

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

Double-Blind Phase

- Prematurely discontinued double-blind study treatment (with summary of reasons for discontinuing treatment)
- Completed double-blind study treatment

Open-Label Phase

- Willing to enter open-label phase
- Entered open-label phase
- Prematurely discontinued open-label study treatment (with summary of reasons for discontinuing treatment)
- Completed open-label study treatment

TFFU Phase

- Entered TFFU period
- Completed TFFU
- Discontinued TFFU

Study Completion

- Remaining on study
- Prematurely discontinued study (with summary of reasons for discontinuing study)
- Started another HBV therapy
- Completed protocol-planned duration of the study

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

4.3. Extent of Exposure

Exposure data described below will be summarized for the double-blind phase and open-label phase separately.

4.3.1. Duration of Exposure to Blinded Study Drug

Duration of exposure to blinded study drug will be defined as (last dose date of blinded study drug – first dose date of blinded study drug + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to 1 decimal place, eg, 4.5 weeks). If subjects are still on blinded study drug, the latest of blinded study drug start and end dates, and the clinic and laboratory visit dates (excluding the open-label and 24-week treatment-free follow-up visit dates) will be used to impute the last dose date of blinded study drug for calculating the duration of blinded study drug exposure.

Duration of exposure to blinded study drug will be summarized using descriptive statistics (sample size, mean, standard deviation [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), etc.

Summaries will be provided by treatment group for subjects in the Safety Analysis Set.
No inferential statistics will be provided.

4.3.2. Adherence with Blinded Study Drug Regimen

Study drug regimen adherence will be computed based on tablet counts for the active drug only (eg, adherence in TAF group only includes TAF and not placebo for TDF). The numbers of tablets of study drug dispensed and returned are captured on study drug accountability forms.

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

$$\text{Adherence (\%)} = 100 \times \frac{\text{Number of tablets taken}}{\text{Number of tablets prescribed}}$$

$$= 100 \times \frac{\sum \text{No. of tablets taken at each dispensing period [1]}}{\left(\sum \text{No. of tablets prescribed at each dispensing period [2]}\right) + 1}$$

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

[2] Number of tablets prescribed at a distinct dispensing period for a study drug is calculated as the daily number of tablets prescribed for the study drug multiplied by **the duration of treatment** at the dispensing period of the same dispensing date. Total number of tablets prescribed is determined by summing the number of tablets prescribed 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 the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) **next dispensing date** of the study drug, minus dispensing date of the study drug.

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

For a record where the number of tablets returned was missing (with "Yes" answered for "Was bottle returned?" question), it is assumed the number of tablets returned was 0. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Adherence up to the Week 144 Visit will be calculated for subjects in the Safety Analysis Set.

The number and percentage of subjects who return at least 1 bottle and have calculable adherence during the study, descriptive statistics for adherence up to Week 144 visit for a study drug regimen (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

4.3.3. Duration of Exposure to Open-Label Study Drug

Duration of exposure to open-label study drug will be summarized for participants in the Open-Label Safety Set. It is defined as (Last Dose Date of Open-Label Study Drug – First Dose Date of Open-Label Study Drug + 1) / 7 in weeks, regardless of temporary interruptions in study drug administration, and will be summarized using descriptive statistics (ie, sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum and maximum) by treatment group. The number and percentage of participants exposed will be summarized by prespecified period, eg, ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), etc.

If participants are still on open-label study drug at the time of the data-cut, the latest date of the open-label study drug start and end dates, the clinic visit dates, and laboratory visit dates (excluding the 24-week TFFU visit dates) will be used to impute the last dose date of the open-label study drug for calculating the duration of the open-label study drug exposure.

4.3.4. Adherence with Open-Label Study Drug Regimen

Study drug regimen adherence will be computed based on tablet counts for open-label study drug for participants in the Open-Label Safety Set. The numbers of tablets of open-label study drug dispensed and returned are captured on study drug accountability forms. The same formula used for the adherence of double-blind study drug regimen will be used for the calculation of adherence to the open-label study drug regimen.

The duration of treatment at a dispensing period for the open-label study drug is calculated as the minimum of (a) the last returned date of the same dispensing period for the open-label study drug, (b) date of premature discontinuation of open-label study drug, and (c) **next dispensing date** of open-label study drug, minus the dispensing date of the open-label study drug.

The next dispensing date is the following dispensing date of open-label study drug regardless of the bottle return date.

For a record where the number of tablets returned was missing (with “Yes” answered for “Was bottle returned?” question), it is assumed the number of tablets returned was 0. If the number of tablets dispensed was missing or any open-label study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then all records for the same dispensing date for the open-label study drug will be excluded from both denominator and numerator calculation.

Adherence for open-label study drug will be calculated using all data from the entire open-label dosing period up to the date of permanent discontinuation of the open-label study drug for participants who prematurely discontinued open-label study drug, or completed open-label study drug.

The number and percentage of participants who return at least 1 bottle and have calculable adherence during the open-label phase, descriptive statistics for adherence up to the visits mentioned above for the open-label study drug (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group for the Open-Label Safety Analysis Set. No inferential statistics will be provided.

4.4. Protocol Deviations

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations (e.g., at least 1, with 1, 2, 3 or more important protocol deviations), and the total number of important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by treatment group for the Full Analysis Set. A by participant listing will be provided for those participants with important protocol deviations. A listing of participants who received the wrong study treatment will also be provided.

4.5. Assessment of COVID-19 Impact

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

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

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

4.5.2. Protocol Deviations Due to COVID-19

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

4.5.3. Missed and Virtual Visits due to COVID-19

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

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 2.

4.5.4. 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-participant listing of AEs of COVID-19 will be provided if applicable.

4.5.5. Overall Assessment of COVID-19 Pandemic Impact

For participants affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 SMQ narrow search
- Specific adverse event directly associated with the pathogen causing COVID-19, as determined by Medical Search Term (MST)
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed key assessments due to COVID-19 (Key assessments are the assessments contributing to primary and key secondary end points which happened before COVID-19 pandemic)

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death and specific adverse event.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic data (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, body weight, height, body mass index [BMI], and Vitamin D) will be summarized by treatment group and overall, using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. Age is calculated as age in years at the first dose of study drug.

In addition, the following baseline characteristics and medical history will be summarized:

- BMI categories (< 18.5 kg/m^2 [underweight], ≥ 18.5 - 25.0 kg/m^2 [normal], ≥ 25.0 - 30.0 kg/m^2 [overweight], and ≥ 30.0 kg/m^2 [obese])
- HBV DNA (log_{10} IU/mL)
- HBV DNA categories (< 7 log_{10} IU/mL, ≥ 7 log_{10} IU/mL - < 8 log_{10} IU/mL, ≥ 8 log_{10} IU/mL)
- ALT (U/L)
- ALT level based on central laboratory normal range (≤ ULN, > ULN - 5 × ULN, > 5 × ULN - 10 × ULN, > 10 ULN)
- ALT level 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 (≤ ULN, > ULN - 5 × ULN, > 5 × ULN - 10 × ULN, > 10 ULN)
- Estimated GFR by CG, CKD-EPI creatinine, and CKD-EPI Cystatin C methods
- HBeAg status (positive, negative)
- Previous oral nucleoside/nucleotide treatment experience (yes, no)
- Previous interferon experience (yes, no)
- Years positive for HBV
- HBV Genotype (A, B, C, D, E, F, etc)
- FibroTest score
- Fibrosis stage by fibrotest score (0 - 0.48, 0.49 - 0.74, 0.75 - 1)
- Cirrhosis history (yes, no, indeterminate/unknown)

- Proteinuria by urinalysis (dipstick) (Grade 0, Grade 1, Grade 2, Grade 3)
- Medical history: diabetes mellitus (yes, no), hypertension (yes, no), cardiovascular disease (yes, no), and hyperlipidemia (yes, no)
- Clinical BMD status (normal, osteopenia, osteoporosis)
- IL28B Genotype

Diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia above are determined by medical history and/or concomitant medication data, which will be reviewed by the Gilead medical monitor before unblinding.

5.2. Medical History

A listing of medical history data will be provided for the Randomized Analysis Set.

6. EFFICACY ANALYSES

For the final analyses, efficacy data will be summarized for the double-blind and open-label phase up to Week 384 using Missing = Failure (M = F) based on participants in the FAS and Missing = Excluded (M = E) approach based on participants in the FAS if applicable.

No statistical comparisons will be performed for the efficacy analyses. All efficacy data up to the week 384 (i.e., final) data finalization including data collected during 24-week TFFU period for participants who prematurely discontinued study drug will be listed.

HBV DNA lab values based on the Roche COBAS® Taqman® assay (with LLOQ of 29 IU/mL, on or before Week 64 visit), Roche AmpliPrep/COBAS® TaqMan® 2.0 assay (with LLOQ of 20 IU/mL, after Week 64 visit) and Roche COBAS 6800 assay (with LLOQ of 10 IU/mL, at Week 360 and 384 visits) will be used for HBV DNA analysis. If the value in IU/mL (TaqMan) is above the upper limit of quantification, the corresponding diluted value (TaqDil), if available, will be used.

6.1. Primary Efficacy Endpoints

The primary efficacy end point is the proportion of participants with HBV DNA < 29 IU/mL at Week 48, which has been analyzed in the previous Week 48 interim analysis, and will not be repeated for this final analysis (refer to Week 48 SAP for the statistical analysis method for the primary efficacy end point).

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

For the definitions below, double-blind baseline will be used.

The secondary efficacy end points are as follows:

- The proportion of participants with plasma HBV DNA < 29 IU/mL at Weeks 96, 144, 240, and 384
- The proportion of participants with plasma HBV DNA < 29 IU/mL (target not detected) at Weeks 48, 96, 144, 240, and 384
- The proportion of participants with ALT normalization (by central laboratory and AASLD criteria) at Weeks 48, 96, 144, 240, and 384
- The proportion of participants with HBsAg loss at Weeks 48, 96, 144, 240, and 384
- The proportion of participants with HBsAg seroconversion to anti- HBs at Weeks 96, 144, 240, and 384

- The change from baseline in fibrosis as assessed by FibroTest® at Weeks 48, 96, 144, 240, and 384
- The incidence of drug resistant mutations at Weeks 48, 96, 144, 240, and 384
- The change from baseline in $\log_{10}$ (HBV DNA) (IU/mL) at Weeks 48, 96, 144, 240, and 384
- The change from baseline in $\log_{10}$ (HBsAg) (IU/mL) at Weeks 48, 96, 144, 240, and 384
- The change from baseline in ALT at Weeks 48, 96, 144, 240, and 384

Incidence of drug resistant mutations will be reported in a separate virology report.

For the final analysis, the following definitions will be used:

- HBsAg loss is defined as HBsAg test result changes from HBsAg positive at baseline to HBsAg negative at a postbaseline visit with baseline HBsAb negative or missing
- HBsAg seroconversion is defined as HBsAg loss and HBsAb test result changes from HBsAb negative or missing at baseline to HBsAb positive at a postbaseline visit
- ALT normalization is defined as ALT > ULN (by central laboratory normal range or AASLD normal range) at baseline but within normal range at a postbaseline visit

Both baseline and postbaseline borderline 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

6.2.2. Analysis Methods for Secondary Efficacy End points

The analyses for the secondary efficacy endpoints will be conducted using the FAS. All the secondary efficacy endpoints involving proportions will be analyzed using the same statistical method (M = F) applied to the analysis of the primary efficacy endpoint. Sensitivity analyses will be performed using the M = E approach as well. No statistical comparisons will be performed.

The change from baseline in log10 (HBV DNA) (IU/mL), log10 (HBsAg) (IU/mL), and ALT will be summarized by visit using observed data (ie, missing will be excluded). In addition, the proportion of participants with HBV DNA < 29 IU/mL (M = F and M = E), ALT normalization (M = F and M = E), mean change from double-blind baseline in log10 (HBV DNA) (IU/mL), log10 (HBsAg) (IU/mL), and ALT (U/L) will be plotted over time for participants in the FAS.

Fibrosis assessed by FibroTest® at each visit and the change from baseline in FibroTest score will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group. A shift table of fibrosis stage based on FibroTest score by visit will also be provided. Mean change from double-blind baseline in FibroTest score will be plotted with 95% CI over time using observed data for participants in the FAS. No statistical comparisons will be performed. A listing of fibrosis assessment by FibroTest® will also be provided.

6.3. Changes From Protocol-Specified Efficacy Analyses

Change from baseline in $\log_{10}$ (HBV DNA) (IU/mL), $\log_{10}$ (HBsAg) (IU/mL), and ALT were added in the SAP as secondary efficacy end points to fully explore the treatment effect of TAF versus TDF. The Randomized Analysis Set was not defined in the protocol but is added in the SAP. All these changes which were previously documented in the Week 48 China Analysis SAP have been carried over to this SAP.

7. SAFETY ANALYSES

For the Final analysis, cumulative safety data (AEs, laboratory abnormalities, etc.) and exposure data will be summarized for (1) participants in the Safety Analysis Set during the double-blind phase, (2) participants in the Open-Label Safety Analysis Set during the open-label phase.

By-visit summary tables will be presented for the entire study treatment period (double-blind and open-label phase combined), based on participants in the Safety Analysis Set, starting from the double-blind phase baseline. No by-visit summaries for safety measurements will be generated for the TFFU phase.

For the analyses of events occurring during open-label phase, baseline will be reset as the last nonmissing value obtained on or prior to Open-Label Study Day 1 except for DXA BMD, which is defined as the last nonmissing value obtained on or prior to Open-Label Study Day 14.

All safety data, including data collected during the TFFU period for participants prematurely discontinued study drug, will be included in data listings.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be attached to the clinical database.

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 Appendix 5 of the clinical study protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of AEs to Study Drug

Related AEs are those for which the investigator answers “Yes” to the question “Related to Study Treatment?” in the eCRF. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. Data listings will show relationship as missing.

7.1.4. Relationship of AEs to Study Procedure

AEs for which ‘Yes’ is marked for question ‘Related to Study Procedures?’ in the eCRF will be identified and included in AE listing.

7.1.5. Serious AEs

Serious AEs are those identified as serious in the eCRF, where 'Yes' was marked for 'AE serious'. The clinical database will be reconciled with the serious AE database (from the Drug Safety and Public Health Department) before database finalization.

7.1.6. Treatment-Emergent AEs

7.1.6.1. Definition of Treatment-Emergent

Summaries of treatment-emergent AEs are defined for the double-blind and the open-label phases separately.

Treatment-emergent AEs occurring during the double-blind phase are defined as:

- Any AE with an onset date on or after the blinded study drug start date and no later than the blinded study drug stop date for those who discontinued blinded study drug, or
- Any AE leading to blinded study drug discontinuation.

Treatment-emergent AEs occurring during the open-label phase are defined as:

- Any AE with an onset date on or after the open-label study drug start date and no later than the open-label study drug stop date + 3 days for those who discontinued open-label study drug, or
- Any AE leading to open-label study drug discontinuation.

7.1.6.2. Incomplete Dates

If an AE onset date is incomplete or completely missing, the following rules will be used to define treatment-emergent AE during the double-blind and open-label phases:

<u>Events with Missing Onset Day and/or Month</u>

The event is treatment-emergent during the double-blind phase if the following criteria are met:

- The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of the blinded study drug, and
- For those who discontinued the blinded study drug permanently only: the month and year (or year) of onset date is the same as or before the month and year (or year) of the date of the last dose of the blinded study drug, and
- End date is as follows:
  - The (complete) end date is on or after the first dose date of the blinded study drug, or
  - The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of the blinded study drug, or
  - End date is completely missing

The event is treatment-emergent during the open-label phase if the following criteria are met:

- The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of the open-label study drug, and
- For those who discontinued the open-label study drug permanently only: the month and year (or year) of onset date is the same as or before the month and year (or year) of the date of the last dose of the open-label study drug + 3 days, and
- End date is as follows:
  - The (complete) end date is on or after the first dose date of the open-label study drug, or
  - The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of the open-label study drug, or
  - End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as treatment-emergent AE during the double-blind phase if end date is as follows:

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

An AE with a completely missing onset date is defined as treatment-emergent AE during the open-label phase if end date is as follows:

- The (complete) end date is on or after the first dose date of the open-label study drug, or
- The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of the open-label study drug, or
- End date is completely missing

7.1.7. Summaries of AEs and Deaths

Adverse events will be summarized for (1) participants in the Safety Analysis Set during the Double-Blind phase, and (2) participants in the Open-Label Safety Analysis Set during the open-label phase. The full set of AE summaries as described below will be generated for both (1) and (2).

A brief summary of AEs (ie, the number and percentage of participants) will be presented by treatment group for the double-blind and open-label phases separately for the following: (1) any treatment-emergent AE, (2) any Grade 3 or 4 treatment emergent AE, (3) any Grade 2, 3 or 4 treatment-emergent AE, (4) any treatment emergent study drug-related AE, (5) any Grade 3 or 4 treatment-emergent study drug-related AE, (6) any Grade 2, 3 or 4 treatment-emergent study drug-related AE, (7) any treatment-emergent serious adverse event (SAE), (8) any treatment-emergent study drug-related SAE, (9) any treatment-emergent AE leading to premature study drug discontinuation, (10) any treatment emergent AE leading to dose modification or study drug interruption, and (11) any treatment-emergent death.

Treatment-emergent death refers to death that occurs between the first dose date and the last dose date + 3 days (inclusive).

Summaries (number and percentage of participants) of AEs (by SOC, HLT [if specified below], and PT) will be provided by treatment group and overall for the double-blind phase on Safety Analysis Set and the open-label phase based on the Open-Label Safety Analysis Set as follows:

- All treatment-emergent AEs summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent AEs
- Any Grade 2, 3, or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AE summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs leading to premature discontinuation from study drug
- All treatment-emergent AEs leading to dose modification or study drug interruption

Multiple events will be counted once only per participant in each summary. For data presentation, SOC (and HLT) will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All AEs (including AEs in the TFFU phase)
- Grade 3 and 4 AEs

- SAEs
- Study drug-related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to dose modification or study drug interruption

7.1.8. Potential Uveitis Events

Analysis will be performed to detect AEs where the symptoms reported may potentially represent uveitis. The list of PTs for potential uveitis events were defined as events from the predefined MST list consisting of ocular PTs, initially reviewed by an external ophthalmologist, and maintained by Patient Safety (PS) through MedDRA upversioning for safety monitoring of posterior uveitis.

A summary (number and percentage of participants) of treatment-emergent potential uveitis events by PT will be provided by treatment group for the double-blind phase on Safety Analysis Set and the open-label phase based on the Open-Label Safety Analysis Set. A data listing of potential uveitis events will be provided.

7.1.9. Potential Cardiovascular Events

Potential cardiovascular events are defined as events with predefined list of MedDRA PTs based on 3 MedDRA SMQs based on the latest MedDRA version: Ischemic central nervous system vascular conditions, Other ischemic heart disease, and Myocardial infarction.

A summary (number and percentage of participants) of potential treatment-emergent cardiovascular events and serious cardiovascular events by PT will be provided by treatment group for the double-blind phase on Safety Analysis Set and the open-label phase based on the Open-Label Safety Analysis Set. data listing of potential cardiovascular 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 graded laboratory data will be provided for double-blind phase on Safety Analysis Set and the open-label phase based on the Open-Label Safety Analysis Set. Summaries of numerical laboratory data by visit will be provided for the entire study period for participants in the Safety Analysis Set from baseline to Week 384.

The analyses will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.4.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, urine chemistry, and urinalysis separately. Values falling outside of the relevant 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 (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for each laboratory test during the entire study period specified in the study protocol as follows:

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

Median (Q1, Q3) change from the double-blind baseline in selected safety end points including the fasting lipid panel parameters, and fasting glucose over time will be plotted by treatment group for the entire study treatment period (double-blind and open-label phases combined), for participants in the Safety Analysis Set.

7.2.1.1. Metabolic Assessments

For the lipid panel and glucose measurements, only those under fasting status will be summarized.

Fasting lipid data (including total cholesterol, LDL, HDL and triglycerides) will also be analyzed using the following National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III categories {National Cholesterol Education Program (NCEP) 2001}:

- **For total cholesterol (mg/dL):** < 200 (desirable), 200-239 (borderline high), and ≥ 240 (high)
- **For LDL (mg/dL):** < 100 (optimal), 100-129 (near optimal/above optimal), 130-159 (borderline high), 160-189 (high), and ≥ 190 (very high)
- **For HDL (mg/dL):** < 40 (low), 40-59 (normal), and ≥ 60 (high)
- **For triglycerides (mg/dL):** < 150 (normal), 150-199 (borderline high), 200-499 (high), and ≥ 500 (very high)

The number and proportion of participants for the above categories of each lipid parameter will be summarized by its baseline category for each treatment group at each visit for the entire study treatment period.

7.2.1.2. Calcium Corrected for Albumin

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

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

When albumin value is ≥ 4.0 g/dL, the actual calcium results will be used. Toxicity grading for calcium will be applied based on the corrected values.

7.2.2. Graded Laboratory Values

The criteria specified in the protocol will be used to grade laboratory results as Grade 0, Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life-threatening). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analysis for each direction (ie, increased, decreased) will be presented separately.

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

If any laboratory toxicity grading scale overlaps with normal reference ranges (eg, Grade 1 scale overlaps with normal reference ranges), laboratory values within normal range will not be graded except for lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities occurring in the double-blind phase are defined as values that increase by at least 1 toxicity grade from baseline at any postbaseline visit up to and including the last does date of the blinded study drug (or 'last dose date of the blinded study drug + 1' for those who enter the open-label phase) for those who discontinued blinded study drug permanently, or values that increase by at least 1 toxicity grade from baseline at any postbaseline visit for those who are still on the blinded study drug. If the relevant baseline laboratory data are missing, any laboratory abnormality of at least Grade 1 will be considered treatment-emergent.

Treatment-emergent laboratory abnormalities occurring in the open-label phase are defined as values that increase by at least 1 toxicity grade from the open-label baseline at any open-label postbaseline visit up to and including the last dose date of open-label study drug + 3 days for those who discontinued open-label study drug prematurely (or 'last dose date of the open-label study drug + 3 days' for those who completed the open-label phase), or values that increase by at least 1 toxicity grade from the open-label baseline at any open-label postbaseline visit for those who are still on the open-label study drug. For the analyses of abnormalities occurring during open-label treatment, baseline will be the last available record on or prior to Open-Label Study Day 1.

Fasting glucose and nonfasting glucose are graded based on different grading scales. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Since nonfasting glucose was not assessed at baseline, the maximum postbaseline grade will be summarized.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities occurring in the double-blind phase are defined as values that worsen by at least 3 grades from baseline at any postbaseline visit up to and including the last dose date of the blinded study drug for those who discontinued blinded study drug prematurely (or 'last dose date of the blinded study drug + 1 day' for those who completed double -blind phase), or values that worsen by at least 3 grades from baseline at any postbaseline visit for those who are still on blinded study drug. If relevant baseline laboratory data are missing, any laboratory abnormalities of at least Grade 3 or 4 will be considered as treatment-emergent marked laboratory abnormalities.

Treatment-emergent marked laboratory abnormalities occurring in the open-label phase are defined as values that worsen by at least 3 grades from the open-label baseline at any open-label postbaseline visit up to and including the last dose date of open-label study drug + 3 days for those who discontinued open-label study drug prematurely (or 'last dose date of the open-label study drug + 3 days' for those who completed the open-label phase), or values that worsen by at least 3 grades from the open-label baseline at any open-label postbaseline visit for those who are still on open-label study drug.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) of laboratory abnormalities will be provided by treatment group (participants categorized according to most severe abnormality grade) for the double-blind and open-label phase:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with any nonmissing postbaseline (or open-label postbaseline) value in the given study period. A listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided.

7.2.3. 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 consecutive postbaseline visits. All treatment-emergent ALT elevations including confirmed ALT elevations will be summarized for the double blind and the open-label phases separately. For analyses of ALT elevation during open-label treatment, baseline will be the last available record on or prior to Open-Label Study Day 1. All treatment emergent and nontreatment-emergent ALT elevations will be included in a listing.

7.3. Bone Safety Analyses

The BMD-related analyses for the entire study treatment period will be based on participants in the Hip or Spine DXA Analysis Set. The analyses of fracture events and bone events during double-blind phase will be based on the Safety Analysis Set, and the summaries for the open-label phase will be based on Open-Label Safety Analysis Set.

7.3.1. Bone Mineral Density (BMD)

Observed BMD values will be used for all the analyses described below: Percentage change from baseline in hip BMD and spine BMD during the entire study treatment period will be summarized by treatment group and visit using descriptive statistics for participants in the Hip and Spine DXA Analysis Sets.

For each participant and each visit, the clinical BMD status will be defined for hip and spine BMD based on the corrected t-score in Table 7-1.

Table 7-1. Normal, Osteopenia, and Osteoporosis as Defined by T-Score

Clinical Status	BMD T-Score
Normal	t-score ≥ -1.0
Osteopenia	-2.5 ≤ t-score < -1.0
Osteoporosis	t-score < -2.5

The number and percentage of participants in each clinical BMD status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine.

The number and percentage of participants in each category based on percentage change from baseline in hip BMD and spine BMD (> 7% decrease, > 5% to ≤ 7% decrease, > 3% to ≤ 5% decrease, > 1% to ≤ 3% decrease, > 0 to ≤ 1% decrease, 0 to ≤ 1% increase, > 1% to ≤ 3% increase, > 3% to ≤ 5% increase, > 5% to ≤ 7% increase, > 7% increase) will be summarized by treatment group and visit.

The number and percentage of participants in each category based on percentage change from baseline in femoral neck (≥ 7% decrease, ≥ 5% to < 7% decrease, ≥ 3% to < 5% decrease, ≥ 1% to < 3% decrease, ≥ 0 to < 1% decrease, ≥ 0 to < 1% increase, ≥ 1% to < 3% increase, ≥ 3% to < 5% increase, ≥ 5% to < 7% increase, ≥ 7% increase) will be summarized by treatment group and visit.

Median (Q1, Q3) and mean (95% CIs) of percentage change from the double-blind baseline in observed hip BMD and spine BMD over time will be plotted by treatment group for the entire study treatment period for participants in the DXA Analysis Set.

7.3.2. Bone Biomarkers

Bone biomarkers include serum CTX, P1NP, PTH, OC, and bsAP.

Baseline, postbaseline, change from baseline, and percentage change from baseline in bone biomarkers will be summarized by treatment group and visit using descriptive statistics.

Median (Q1, Q3) percentage change from the double-blind baseline in each bone biomarker over time will be plotted by treatment group for the entire study treatment period for participants in the Safety Analysis Set.

7.3.3. Fracture Events

The PTs for fracture events were defined based on HLGT of Fractures from latest version of MedDRA. The number and percentage of subjects who experienced fracture events will be summarized by treatment group for the double-blind and the open-label phase separately. A data listing of fracture events will be provided.

7.3.4. Bone Events

The PTs for bone events were defined based on the broad search for bone mineral density and bone-disorder-related PTs, including fractures, using the latest version of MedDRA. The number and percentage of participants who experienced treatment-emergent bone events will be summarized by treatment group for the double-blind and the open-label phase separately. A data listing of bone events will be provided.

7.4. Renal Safety Analyses

7.4.1. Confirmed Renal Abnormalities

Confirmed renal abnormalities are defined as follows:

- Confirmed increase from baseline in creatinine of at least 0.5 mg/dL or
- Confirmed CL_{Cr} by CG below 50 mL/min or
- Confirmed phosphorus < 2 mg/dL

Treatment-emergent confirmed renal abnormalities will be summarized for the double-blind and the open-label phase separately. For analyses of confirmed renal abnormalities during the open label treatment, baseline will be the last available record on or prior to Open-Label Study Day 1.

All confirmed renal abnormalities including those that occur during the TFFU period will be listed.

7.4.2. Serum Creatinine

The baseline and change from baseline in serum creatinine will be summarized using descriptive statistics.

Median (Q1, Q3) and mean (95% CIs) of change from the double-blind baseline in observed serum creatinine over time will be plotted by treatment group for the entire study treatment period for participants in the Safety Analysis Set.

A positive shift in serum creatinine values was observed due to a lot calibration change on 01 July, 2018, occurring across Covance laboratory sites worldwide. A correction was therefore applied to records on or after 01 July, 2018 to serum creatinine, following the regression equation specified in Table 7-2. The corrected serum creatinine values will be used for the analyses of serum creatinine, serum creatinine toxicity, eGFR estimated by the Cockcroft Gault formula, eGFR by the CKD-EPI method and other relevant parameters.

The corrected values must be in the same unit as the original values after going through the regression formula in Table 7-2.

- If the unit of serum creatinine is "µmol/L", then use the formula directly.
- If the unit of serum creatinine is "mg/dL", the values should be converted to "µmol/L" before using the formula.

After the correction, unit of serum creatinine should be converted back to "mg/dL" for summary and comparison purpose.

Table 7-2. Method of Serum Creatinine Correction

Regional Lab Center	Accession Number[a]	Regular Regression for Serum Creatinine (µmol/L)[b, c]
Indianapolis	starts with 65	Y=1.002×X+1.77
Geneva	starts with 62 or 63	Y=1.025×X+2.62
Shanghai	starts with 67	Y=0.971×X+5.42
Singapore	starts with 64 or 66	Y=1.009×X−1.42
Japan	start with 68	Y=1.033×X+7.25

a Accession numbers specified which regional lab center tested the sample. For example, samples with accession number starting with 65 were tested in Indianapolis Auto Chemistry Center.
b X and Y are the serum creatinine values from previous lot before 01 July, 2018 and serum creatinine values from new lot on or after 01 July, 2018, respectively.
c The serum creatinine correction is based on the unit of umol/L. The unit should be converted to mg/dL for summary purposes.

7.4.3. Estimated Glomerular Filtration Rate

The following formulae 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 actual total body mass in kilograms, and SCr is serum creatinine.

- CKD-EPI Creatinine Based:

  $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2) = 141 × $\min(SCr/\kappa,1)^{\alpha}$ × $\max(SCr/\kappa,1)^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black),

  where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1 {Levey 2009}.

- CKD-EPI Cystatin C based:

  $eGFR_{CKD\text{-}EPI,\ cysC}$ (mL/min/1.73 m^2) = 133 × min(SCys/0.8, 1)$^{-0.499}$ × max(SCys/0.8, 1)$^{-1.328}$ × 0.996^{age} [× 0.932 if female],

  where SCys is serum cystatin C.

Change from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at each postbaseline visit during the entire study treatment period will also be provided.

The number and proportion of participants with decrease from baseline of ≥ 25% and ≥ 50% in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ will be summarized by treatment groups for the double-blind phase and the open-label phase. Baseline for the open-label phase will be the last available record on or prior to the first dose date of open-label study drug.

The number and proportion of participants in each stage of chronic kidney disease (CKD) will be summarized by double-blind baseline stages of CKD at the entire study period based on participants in the Safety Analysis Set.

The stages of CKD are defined as follows:

- **Stage 1:** $eGFR_{CG}$ ≥ 90 mL/min
- **Stage 2:** $eGFR_{CG}$ ≥ 60 and < 90 mL/min
- **Stage 3:** $eGFR_{CG}$ ≥ 30 and < 60 mL/min
- **Stage 4:** $eGFR_{CG}$ ≥ 15 and < 30 mL/min
- **Stage 5:** $eGFR_{CG}$ < 15 mL/min

Cystatin C will be collected for each participant at baseline visit (Amendment 2 and after) and whenever their postbaseline eGFR by CG < 50 mL/min. Therefore, $eGFR_{CKD\text{-}EPI,\ cysC}$ will be summarized as the baseline disease characteristics only. All postbaseline $eGFR_{CKD\text{-}EPI,\ cysC}$ with percentage change from baseline will be listed.

Median (Q1, Q3) change from the double-blind baseline in eGFR by CG and CKD-EPI creatinine methods over time will be plotted by treatment group for the entire study treatment period (double-blind and open-label phases combined) for participants in the Safety Analysis Set.

7.4.4. Treatment-Emergent Proteinuria (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) will be summarized by treatment group for the double-blind and the open-label phase separately. A listing of participants with treatment-emergent proteinuria will be provided.

7.4.5. Urine Creatinine, Urine RBP to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

Baseline, postbaseline, change from baseline and percentage change from baseline in urine creatinine, urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by treatment group and visit using descriptive statistics, during the entire study treatment period.

Median (Q1, Q3) percentage change from the double-blind baseline in the 2 ratios over time will be plotted by treatment group for the entire study treatment period, for participants in the Safety Analysis Set.

7.4.6. Proteinuria by Quantitative Assessment

Baseline, postbaseline, changes from baseline, and percentage change from baseline in UPCR and UACR will be summarized by treatment group and visit using descriptive statistics, for the entire study treatment period.

The number and proportion of participants with UPCR ≤ 200 mg/g versus > 200 mg/g will be summarized by baseline category for each postbaseline visit during the entire study treatment period {KDIGO Guideline Development Staff 2013}.

The number and proportion of participants with UACR < 30 mg/g versus ≥ 30 mg/g will be summarized by baseline category for each postbaseline visit during the entire study treatment period {KDIGO Guideline Development Staff 2013}.

Median (Q1, Q3) percentage change from the double-blind baseline in the 2 ratios over time will be plotted by treatment group for the entire study treatment period for participants in the Safety Analysis Set.

7.4.7. Other Renal Biomarkers

Other renal biomarkers include TmP/GFR, $FEPO_4$, and FEUA.

TmP/GFR based on serum creatinine {Barth 2000} will be calculated as follows:

$$TmP/GFR = TRP \times SPO_4 \quad if\ TRP \le 0.86$$
$$TmP/GFR = 0.3 \times TRP / \left[1 - (0.8 \times TRP)\right] \times SPO_4 \quad if\ TRP > 0.86$$

where TRP (tubular reabsorption of phosphate) is calculated by:

$$TRP = 1 - \frac{UPO_4}{SPO_4} \times \frac{SCr}{UCr}$$

where SCr is serum creatinine concentration (mg/dL), UPO_4 is urine phosphate concentration (mg/dL), SPO_4 is serum phosphate concentration, and UCr is urine creatinine concentration (mg/dL).

Urine FEPO4 will be calculated as follows:

$$FEPO_4\ (\%) = (SCr \times UPO_4) / (SPO_4 \times UCr) \times 100\ (\%)$$

Urine FEUA will be calculated as follows:

$$FEUA\ (\%) = (SCr \times UUa) / (SUa \times UCr) \times 100\ (\%)$$

Where UUa and SUa are urine and serum uric acid (mg/dL), respectively.

The baseline, postbaseline, and change from baseline in TmP/GFR, $FEPO_4$, and FEUA will be summarized by treatment group and visit using descriptive statistics, during the entire study treatment period.

Median (Q1, Q3) change from the double-blind baseline in TmP/GFR, $FEPO_4$, and FEUA over time will be plotted by treatment group for the entire study treatment period, for participants in the Safety Analysis Set.

7.5. Ophthalmologic Assessment

As no Ophthalmologic assessment was performed in China, no analysis will be conducted.

7.6. Body Weight

Body weight at each visit and change from baseline in body weight will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group for each postbaseline analysis window, during the entire study treatment period. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

7.7. Prior Hepatitis B Medications

Prior HBV medications will be summarized by treatment group. No inferential statistics will be computed. A listing of prior HBV medications will also be provided.

7.8. Concomitant Medications

Concomitant medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications for the double-blind, the open-label phases, and will be summarized (number and percentage of participants) separately by treatment group and WHO drug class and preferred name. Multiple drug use (by preferred name) will be counted only once per participant. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class.

If the start or stop date of concomitant medications is incomplete, the month and year (or year alone if month is not recorded) of start or stop date will be used to determine if the medications are concomitant as follows. The medication is concomitant for the double-blind phase if the month and year of start or stop (or year of the start or stop) of the medication do not meet any of following criteria:

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

The medication is concomitant for the open-label phase if the month and year of start or stop (or year of the start or stop) of the medication do not meet any of following criteria:

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

If both the start and stop date of the medication are missing, the medication will be considered as concomitant during both double-blind and open-label phases.

If the start and stop date of the medications are not missing, and the start date is not after the last dose date of the blinded study drug and the stop date is not before the first dose date of the blinded study drug, or the medications are marked as ongoing and start date is on or before the last dose date of the blinded study drug, the medications are considered concomitant during the double-blind phase.

Similarly, if the start and stop date of the medications are not missing, and the start date is not after the last dose date of the open-label study drug and the stop date is not before the first dose date of the open-label study drug, or the medications are marked as ongoing and start date is on or before the last dose date of the open-label study drug, the medications are considered concomitant during the open-label phase.

Summaries of concomitant medications will be provided for the double-blind phase using the Safety Analysis Set and the open-label phase using the Open-Label Safety Analysis Set. No inferential statistics will be provided. Participants with any concomitant medication use will also be listed.

7.9. Electrocardiogram (ECG) Results

The number and percentage of participants in the Safety Analysis Set with an investigator's ECG assessment of normal, abnormal but not clinically significant, or abnormal and clinically significant will be summarized by treatment group and by baseline result for each visit, during the entire study period. No inferential statistics will be provided.

A by-participant listing of safety ECG results will be provided including treatment, assessment date and time, and ECG results.

7.10. Other Safety Measures

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

Listings of cirrhosis and hepatocellular carcinoma assessment results will be provided.

Alcohol use at baseline will also be listed.

7.11. Changes From Protocol-Specified Safety Analyses

Treatment-emergent proteinuria was not included as a key secondary safety end point in Protocol Amendment 3.1 and is added in the SAP.

As no Ophthalmologic assessment was performed in China, no analysis will be conducted.

Comparison of the safety and tolerability of TAF versus TDF for the treatment of HBeAg negative, CHB beyond Week 48 during the double-blind phase in treatment-naive and treatment-experienced participants was not included as a secondary objective of this study and was documented in the Week 48 China Analysis SAP and is carried over to this SAP.

8. REFERENCES

Barth JH, Jones RG, Payne RB. Calculation of renal tubular reabsorption of phosphate: the algorithm performs better than the nomogram. Ann Clin Biochem 2000;37 (Pt 1):79-81.

KDIGO Guideline Development Staff. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney international. Supplement 2013;3 (1):v-150.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150 (9):604-12.

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

9. SOFTWARE

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

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

10. SAP REVISION

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

11. APPENDICES

Appendix 1. Adverse Events of COVID-19

An adverse event record will be flagged as adverse events for COVID-19 if its Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is included in the pre-specified PT list, which includes all PTs from the narrow search of the following COVID-19 SMQs under based the latest MedDRA version 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 2. 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 11-1). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit" will be assigned as follows:

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

Table 11-1. 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

GS-US-320-0108 SAP Final China

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	20-Dec-2023 18:39:50
PPD	Clinical Development eSigned	04-Jan-2024 16:25:23