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-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
PP	per protocol
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
QD	once daily
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
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 once daily versus tenofovir disoproxil fumarate (TDF) 300 mg once daily for the treatment of HBeAg-negative, chronic hepatitis B (CHB) in treatment-naive and treatment-experienced subjects. For non-China part, 426 subjects were randomized in a 2:1 ratio to the treatment groups, and were stratified by plasma hepatitis B virus (HBV) DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced).

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

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

The duration of double-blind treatment is 144 weeks (96 weeks under Amendment 1 and 2.1). All subjects who complete the double-blind period of treatment are eligible for participation in the open label TAF 25 mg extension period for an additional 240 weeks (through Week 384/ED). Subjects who already entered open label phase at Week 96 per Amendment 2.1 will continue on open label TAF 25 mg QD through Week 384/ED. For the entire duration of the study, subjects and investigators will remain blinded to the initial treatment regimen to which they were randomized.

This statistical analysis plan (SAP) describes the analysis plan for the Week 48 analysis of subjects enrolled in China only.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg versus TDF 300 mg once daily for the treatment of hepatitis B e antigen (HBeAg)-negative, CHB at Week 48 in treatment-naive and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL

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

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

- To compare the safety of TAF 25 mg once daily versus TDF 300 mg once daily 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 once daily versus TDF 300 mg once daily as determined by the change from baseline in serum creatinine at Week 48
- To compare the safety of TAF 25 mg once daily versus TDF 300 mg once daily 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 once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative, CHB in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 96, and 144
- To compare the efficacy of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative, CHB in regard to the proportion of subjects 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 once daily versus TDF 300 mg once daily 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 antibody to HBsAg [anti-HBs]) of TAF 25 mg once daily versus TDF 300 mg once daily 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 once daily versus TDF 300 mg once daily 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 once daily versus TDF 300 mg once daily at Weeks 48, 96, and 144
- To compare the change from baseline in ophthalmologic findings by fundoscopic examination of TAF 25 mg once daily versus TDF 300 mg once daily at Weeks 24, 48, 72, 96, and 144 (or ED visit if prior to Week 144 and more than 24 weeks since prior exam) in a subset of subjects
- 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 subjects receiving TAF or TDF

- To evaluate the comparative open-label efficacy, safety, and drug resistance mutations of TAF 25 mg QD from Week 96 (Amendments 1 and 2.1) or Week 144 (Amendment 3.1) through Week 384 in subjects initially randomized to TAF 25 mg QD and in subjects sequentially treated with TDF 300 mg QD for 96 weeks (Amendments 1 and 2.1) or for 144 weeks (Amendment 3.1) and then switched to open-label TAF 25 mg QD

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

1.2. Study Design

Design Configuration and Subject 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 subjects.

Treatment Groups

For non-China part, subjects were randomized in a 2:1 ratio to the following 2 treatment groups:

- **TAF group:** TAF 25 mg once daily + matched placebo of TDF 300 mg once daily (n = 285)

- **TDF group:** TDF 300 mg once daily + matched placebo of TAF 25 mg once daily (n = 141)

For China, approximately 150 subjects (100 in TAF group and 50 in TDF group) will be enrolled for local registration purposes.

Key Eligibility Criteria

Subjects 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

Study Periods/Phases

The duration of randomized, double-blind treatment is 144 weeks (96 weeks under Amendment 1 and 2.1). At Week 144, all subjects remaining on blinded treatment will be switched to the open-label TAF 25 mg QD extension period for an additional 240 weeks (Week 144 through Week 384/ED). Subjects who already assigned to open-label phase at Week 96 per Amendment 2.1 and consented to Amendment 3.1 later will continue on open-label TAF 25 mg QD through Week 384/ED. All subjects who complete the double-blind period of treatment are eligible for participation in the open-label TAF 25 mg QD extension period. Subjects who permanently discontinue study drug (either prematurely [early discontinuation, ED] or at the end of study [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.

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, 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. At sites in China with the capability only, dual energy x-ray absorptiometry (DXA) scans of the hip and spine will be conducted anytime during the screening period, and should be conducted at least 14 days prior to the first dose of study drug, and will be 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. Hepatic ultrasound for surveillance of hepatocellular carcinoma will be performed starting at Week 96 and then every 24 weeks thereafter until Week 384/ED. Plasma, serum, and urine will be collected at baseline and at every visit thereafter for storage.

Follow-up assessments 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. HBsAg and reflex HBsAb will be evaluated at follow-up Weeks 12 and 24.

Ophthalmologic Substudy

For subjects who provide a separate informed consent (n = 30), a substudy will be conducted to assess ophthalmologic findings, including a fundoscopic examination with slit lamp and retinal photographs (both eyes) prior to the first dose of study drug and at Weeks 24, 48, 72, 96, and 144/ED visits at select sites. An exam should be performed at the ED visit if it is prior to Week 144 and not done within the last 24 weeks of this visit.

Randomization

Subjects 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 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive vs treatment-experienced).

Site and/or Stratum Enrollment Limits

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

Study Duration

The duration of the double-blind treatment is 144 weeks (96 weeks under Amendment 1 and 2.1). All subjects who complete the double-blind period of treatment are eligible for participation in the open label TAF 25 mg extension period for an additional 240 weeks (through Week 384/ED). Subjects already assigned to open label TAF 25 mg QD at Week 96 per Amendment 2.1 will continue on open label TAF 25 mg QD through Week 384/ED. Subjects who permanently discontinue study drug (either prematurely [ED] or at the end of study [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. All subjects in China are currently enrolled under Amendment 3.1 and will complete 3 years of double-blind treatment before rolling over to open-label TAF 25 mg once daily.

Subjects with HBsAg loss with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects 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. Subjects who discontinue study drug for confirmed seroconversion to anti-HBs 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 subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or cirrhosis, should be considered on a case by case basis.

1.3. Sample Size and Power

For China, approximately 150 subjects (100 in TAF group and 50 in TDF group) will be enrolled for local registration purposes.

The sample size and power calculation described below was for non-China subjects. With respect to the primary efficacy endpoint of proportion of subjects 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 subjects with HBV DNA < 29 IU/mL is 0 and the proportion of subjects 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)

These assumptions above 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 Week 48 analysis for Non-China subjects was already conducted after the last subject completed the Week 48 visit or prematurely discontinued study drug. This statistical analysis plan (SAP) describes the analysis plan for the Week 48 analysis of subjects 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 will convene 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.

2.2. Week 48 Analysis (Primary Analysis)

The Week 48 analysis will be conducted after the last subject completes the Week 48 visit or prematurely discontinues study drug.

Further analyses after Week 48 will be conducted if warranted.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

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

3.1.1. Randomized Analysis Set

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

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who have received at least 1 dose of study drug. Subjects will be analyzed according to the treatment they actually received during the double-blinded phase. This is the primary analysis set for safety analyses.

3.1.3. Full Analysis Set (FAS)

The FAS includes all randomized subjects who have received at least 1 dose of study drug. Subjects will be analyzed according to the treatment to which they were randomized during the double-blinded phase. This is the primary analysis set for efficacy analyses.

3.1.4. Per-protocol Analysis Set

The Week 48 Per-Protocol (PP) Analysis Set includes all subjects who (1) were randomized into the study, (2) had received at least 1 dose of study drug, and (3) had not been excluded based on criteria below. Subjects will be analyzed according to the treatment they actually received during the double-blinded phase. The PP analysis set is the secondary analysis set for efficacy analysis.

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

- Subjects who do not have on-treatment HBV DNA in the Week 48 analysis window, except for subjects who discontinue study drug due to lack of efficacy. (Note: lack of efficacy is defined as having the check-box for “Lack of Efficacy” marked as the reason for premature study drug discontinuation on the study drug completion electronic case report form [eCRF] page). The details are summarized in Table 3-1.

Table 3-1. Subjects Excluded from Week 48 PP Analysis Set Due to Premature Discontinuation and/or Missing HBV DNA Assessment in Week 48 Analysis Window

Discontinuation from Study Drug Prior to or on the Upper Bound of Week 48 Analysis Window		HBV DNA Data on Randomized Treatment Available in Week 48 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

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

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the prohibited medications listed in the clinical study protocol (Section 4.3, Table 5.1).
- Subjects with adherence rate for active study drug up to the Week 48 visit below the 2.5th percentile.

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

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

3.1.6. DXA Analysis Set

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

3.1.6.1. Hip DXA Analysis Set

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

3.1.6.2. Spine DXA Analysis Set

The Spine DXA Analysis Set will include all subjects who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline spine BMD values. Subjects will be analyzed according to the treatment they actually received during the double-blinded phase.

3.2. Subject Grouping

For efficacy analysis using FAS and Serologically Evaluable Full Analysis Set, subjects will be analyzed by randomized treatment during the double-blinded phase. For efficacy analysis based on the PP analysis set and safety analysis, subjects will be analyzed by actual treatment received during the double-blinded phase. 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.

3.3. Strata and Covariates

Randomization was stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ 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. Examination of Subject Subgroups

The primary endpoint will be analyzed for the following subject subgroups:

- Age: (a) < 50 years and (b) ≥ 50 years
- Sex: (a) male and (b) female
- Baseline HBV DNA: (a) < 7 $\log_{10}$ IU/mL and (b) ≥ 7 $\log_{10}$ IU/mL
- Oral antiviral treatment status: (a) treatment-naive and (b) treatment-experienced
- Study drug adherence: (a) $< 95\%$ and (b) $\geq 95\%$ (based on adherence up to Week 48 Visit)
- Genotype: (a) B, (b) C, and (c) Other
- Baseline ALT by central laboratory normal range: (a) $\leq$ ULN and (b) $>$ ULN
- Baseline fibrotest score: (a) < 0.75 and (b) ≥ 0.75

3.5. Missing Data and Outliers

3.5.1. Missing Data

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

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

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 an analysis excluding all missing data.

For the 3 key secondary safety endpoints (percentage change from baseline in hip BMD at Week 48, percentage change from baseline in spine BMD at Week 48, change from baseline in serum creatinine at Week 48), an analysis will be performed using the last observation carried forward (LOCF) method to impute missing data.

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

3.5.2. Outliers

Outliers may 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.

3.6. Data Handling Conventions and Transformations

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

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

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (x is considered as the limit of quantitation). 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 limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (x is considered as the limit of quantitation). 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 limit of quantitation).

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).

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.

3.7. Analysis Windows

3.7.1. Definition of Study Day 1 and Other Definitions

Study Day 1 is defined as the day when the first dose of the 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 occurred during 24-week treatment-free follow-up 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 subjects 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 subjects who prematurely discontinued blinded study drug, or for subjects 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 treatment-free follow-up visits will be used to impute the last dose date of blinded study drug.

For subjects 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 subjects 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 subjects who prematurely discontinued open-label study drug or who completed open-label study drug according to Open-Label Study Drug Completion eCRF. If the last dose date is missing (eg, due to lost to follow up) for subjects who prematurely discontinued open-label study drug, or for subjects 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 treatment-free follow-up 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 treatment-free follow-up visit date for subjects who prematurely discontinued study or who completed study according to Study Completion eCRF.

Baseline value is defined as the last nonmissing value obtained on or prior to Study Day 1. For DXA BMD, it is defined as the last value on or prior to Study Day 14.

3.7.2. Analysis Windows

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

The following windows (Table 3-2 to Table 3-8) apply to baseline and on-treatment assessments only, ie, data collected up to the last dose date for those who discontinued study drug prematurely (except efficacy data [HBV DNA, quantitative HBsAg, HBV serology, ALT, fibrotest score] for subjects who discontinue study drug after Week 48 due to HBsAg loss with confirmed seroconversion to anti-HBs), or data collected up to database finalization date for those who have not discontinued study drug permanently.

For subjects 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 3-2, Table 3-3, and Table 3-5).

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 3-2.

Table 3-2. Analysis Windows for HBV DNA, Hematology, Serum Chemistry and Liver Function Tests, Urinalysis, Urine Pregnancy Test, eGFR (by CG and CKD-EPI), PTH, 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 3-3.

Table 3-3. 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 3-4.

Table 3-4. Analysis Windows for BMD Results from DXAand Fasting Lipid Panel

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1(14[a])
Week 24	168	2(15a)	251
Week 48	336	252	419
Week 72	504	420	587
Week 96	672	588	839 (755[b])
Week 120[b]	840	756b	923b
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 subjects who consented to Amendment 3.1.

The analysis windows for serum HBsAg (quantitative) and HBV serology are presented in Table 3-5.

Table 3-5. 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 3-6.

Table 3-6. 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 subjects who consented to Amendment 3.1

The analysis window for serum parathyroid hormone (PTH) is presented in Table 3-7.

Table 3-7. 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 3-8.

Table 3-8. 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

This applies to the subjects who consented to Amendment 3.1.

Data collected after the last dose date will be considered as post-treatment visits. The analysis windows for post-treatment assessments are presented in Table 3-9 and Table 3-10.

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

Visit ID	Nominal Follow-Up Day	Lower Limit	Upper Limit
Follow-Up Week 4	28	1	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 3-10. Analysis Windows for Post-Treatment HBV Serology

Visit ID	Nominal Follow-Up Day	Lower Limit	Upper Limit
Follow-Up Week 12	84	1	125
Follow-Up Week 24	168	126	209

3.7.3. 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, the last available record on or prior to the first dose of study drug will be selected. For DXA BMD, it is defined as the last value on or prior to Study Day 14. If there are multiple records with the same time or no time recorded on the same day for numeric observations, average will be computed for that day, except that for HBV DNA and Quantitative HBsAg, 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 (IU/mL) and Quantitative HBsAg (IU/mL):** 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 non-missing **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 non-missing **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. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects randomized each investigator will be summarized by treatment group and overall using the Safety Analysis Set. Similarly, the number and percentage of subjects enrolled in each randomization stratum will be summarized based on interactive voice response system/web response system (IVRS/IWRS) data.

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

4.2. Disposition of Subjects

The summary of subject disposition will be provided by treatment group and overall. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects in the Randomized Analysis Set, subjects randomized but not treated, subjects in the Safety Analysis Set, and subjects in FAS.

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

Study Drug Completion

- Remaining on double-blind study treatment up to the data-cut date
- Prematurely discontinued double-blind study treatment prior to the data-cut date (with summary of reasons for discontinuing treatment)
- Completed double-blind study treatment up to the data-cut date
- Entered open-label phase up to the data-cut date

Study Completion

- Entered 24-week treatment-free follow-up period up to the data-cut date
- Remaining on study up to the data-cut date
- Prematurely discontinued study prior to the data-cut date (with summary of reasons for discontinuing study)

- Started another HBV therapy up to the data-cut date
- Completed protocol-planned duration of the study up to the data-cut date

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 only.

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.

Time to premature discontinuation of blinded study drug will be analyzed by the Kaplan-Meier method using the Safety Analysis Set. Subjects who completed the blinded study drug will be censored on the last dose date of blinded study drug. Subjects who remain on blinded study drug will be censored on the imputed last dose date of blinded study drug as defined in this section.

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:

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

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

[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** 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 Week 48 visit will be calculated for each subject.

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 48 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.

4.4. Protocol Deviations

A listing will be provided for subjects in the Randomized Analysis Set who violated at least 1 inclusion or exclusion criterion. The listing will include the unmet criteria. A listing of subjects who received the wrong study treatment will also be provided.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex) 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 subjects for categorical data. Age is calculated as age in years at the first dose of study drug. The summaries of demographic data and baseline subject characteristics will be provided for the Safety Analysis Set.

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 19 U/L for female and 30 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)
- HBeAb 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)
- Hip fracture and major osteoporotic fracture probabilities estimated using FRAX® (see Section 7.3.4)
- 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 Week 48 analyses, efficacy data will be summarized for the double-blind phase up to Week 96), with the exception that summaries using M = F approach will be presented up to Week 48 only. All efficacy data up to the Week 48 data-cut including data collected during open-label phase and 24-week treatment-free follow-up period will be listed.

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HBV DNA < 29 IU/mL at Week 48.

6.1.2. Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will be conducted after the last randomized subject reaches Week 48 or discontinues study drug prematurely. An M = F approach will be employed. In this approach, all missing data will be treated as not achieving the primary endpoint (ie, having HBV DNA ≥ 29 IU/mL).The primary analysis will use the FAS.

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

6.1.3. Secondary Analysis for the Primary Efficacy Endpoint

A Missing = Excluded (M = E) approach will be used to summarize proportion of subjects with HBV DNA < 29 IU/mL by visit. In this approach, all missing data will be excluded in the computation (ie, missing data points will be excluded from both the numerator and denominator in proportion computation).

A secondary analysis based on the Week 48 PP analysis set will also be performed to evaluate the robustness of the primary analysis of the primary endpoint.

6.1.4. Subgroup Analysis for the Primary Efficacy Endpoint

The analysis of proportion of subjects who achieved HBV DNA < 29 IU/mL at Week 48 will be repeated within each subgroup specified in Section 3.4 using FAS.

For each level of subgroup factors, the number and percentage of subjects who achieved HBV DNA < 29 IU/mL at Week 48 will be summarized.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

The secondary endpoints beyond Week 96 (Weeks 144, 240, and 384) will not be summarized for the Week 48 analysis. Incidence of drug resistant mutations will be reported in a separate virology report.

For the Week 48 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 will be considered as HBsAg positive and HBeAg positive
- HBsAb and HBeAb borderline will be considered as HBsAb negative and HBeAb negative

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

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.

The change from baseline in $\log_{10}$ (HBV DNA) (IU/mL), $\log_{10}$ (HBsAg) (IU/mL), and ALT will be summarized by visit using observed data (ie, missing will be excluded). In addition, the proportion of subjects with HBV DNA < 29 IU/mL, mean change from baseline in $\log_{10}$ (HBV DNA) (IU/mL), $\log_{10}$ (HBsAg) (IU/mL), and ALT (U/L) will be plotted with 95% CI over time using observed data for 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 baseline in fibrotest score will be plotted with 95% CI over time using observed data for FAS. 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 endpoints to fully explore the treatment effect of TAF versus TDF.

Randomized Analysis Set was not defined in the protocol but is added in the SAP.

7. SAFETY ANALYSES

For Week 48 analysis, safety data will be summarized for the double-blind phase only up to Week 96. The upper limit of the least frequent schedule analysis window of Week 96 (Study Day 839) will be used as Week 96 data cut for cumulative summaries of safety events (eg, treatment-emergent AEs, treatment-emergent laboratory abnormalities). All safety data up to the Week 48 data-cut including data collected during the open-label phase and the 24-week treatment-free follow-up period will be included in data listings.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

AEs 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

AEs 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 purpose. 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

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 study drug stop date for those who discontinued blinded study drug permanently, or
- Any AE with an onset date on or after the blinded study drug start date for those who remain on the 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 for those who discontinued open-label study drug permanently, or
- Any AE with an onset date on or after the open-label study drug start date for those who remain on the 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, 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

A brief summary of AEs (ie, the number and percentage of subjects) will be presented by treatment group 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 (inclusive).

Summaries (number and percentage of subjects) of AEs (by SOC, HLT [if specified below], and PT) will be provided by treatment group and overall using the 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 nonserious AEs occurring in at least 5% of subjects in any treatment group (this summary is generated per requirement for reporting in ClinicalTrials.gov)
- 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 subject 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
- 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 by selecting eye disorder PTs based on MedDRA 19.1, which will be reviewed and edited by an external ophthalmologist for comprehensiveness.

A summary (number and percentage of subjects) of treatment-emergent potential uveitis events by PT will be provided by treatment group based on the 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: Ischemic central nervous system vascular conditions, Other ischemic heart disease, and Myocardial infarction, which was provided by Gilead Drug Safety and Public Health representative and reviewed by Gilead medical monitors.

A summary (number and percentage of subjects) of potential treatment-emergent cardiovascular events and serious cardiovascular events by PT will be provided by treatment group based on the Safety Analysis Set. A data listing of potential cardiovascular events will be provided.

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the Safety Analysis Set. Analysis will be based on values reported in conventional units.

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 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 3.7.3.

Median (Q1, Q3) change from baseline in selected safety endpoints including the fasting lipid panel parameters, and fasting glucose over time will be plotted.

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 subjects for the above categories of each lipid parameter will be summarized by its baseline category for each treatment group at each visit.

In addition, the number and proportion of subjects who took lipid modifying medications at the study entry and initiated the medications will be provided, respectively.

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

A sensitivity analysis of fasting lipid tests (including total cholesterol, LDL, HDL, triglycerides, and total cholesterol to HDL ratio) will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications: baseline, postbaseline, and changes from baseline at Weeks 48 and 96 will be summarized. Only subjects with both baseline and postbaseline values (at Weeks 48 and 96 respectively) will be included in the analysis.

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 occuring 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 prematurely, 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 for those who discontinued open-label study drug prematurely, 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 considered to 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 (or 'last dose date of the blinded study drug + 1' for those who enter the open-label phase) for those who discontinued study drug

prematurely, 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 for those who discontinued open-label study drug prematurely, 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 subjects) of laboratory abnormalities will be provided by treatment group (subjects categorized according to most severe abnormality grade):

- 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 subjects with any nonmissing 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 phase. All treatment-emergent and nontreatment-emergent ALT elevations will be included in a listing.

7.3. Bone Safety Analyses

7.3.1. Bone Mineral Density (BMD)

For BMD analysis during the double-blind phase, any available on-treatment record on or prior to Open-label Study Day 14 will be included into the double-blind phase summary for those who enter the open-label phase after completion of the double-blind phase.

Percentage change from baseline in hip BMD and spine BMD a will be summarized by treatment group and visit using descriptive statistics for subjects in the Hip and Spine DXA Analysis Sets, respectively.

Missing values for hip and spine BMD will be imputed using LOCF up to Week 96 for the analyses of percentage change from baseline. The last on-treatment postbaseline observation will be carried forward to impute the missing value. Baseline observation will not be carried forward.

Percentage change from baseline in observed hip and spine BMD will be analyzed similarly provided up to Week 96.

Observed BMD values will be used for all the analyses described below:

For each subject 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 subjects in each clinical BMD status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine.

For each subject and each visit, percentage change from baseline in hip BMD and spine BMD will be classified into 10 categories: > 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, and > 7% increase. The number and percentage of subjects in each category will be summarized by visit.

Median (Q1, Q3) and mean (95% CI) of percentage change from baseline in observed hip and spine BMD over time will be plotted by treatment group. Listings of hip and spine DXA results will be provided.

7.3.2. Bone Biomakers

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 baseline in bone biomarkers over time will be plotted by treatment group. A listing of bone biomarker data will be provided.

7.3.3. Fracture Events

The PTs for fracture events were defined based on both Standardised MedDRA Query (SMQ) of Osteoporosis/Osteopenia and HLGT of Fractures from MedDRA 19.1. These PTs were reviewed by the Gilead medical monitor before unblinding to identify appropriate fracture event PTs from the SMQ of Osteoporosis/Osteopenia and HLGT of Fractures. Treatment-emergent fracture events will be summarized based on the identified PTs from SMQ alone and both SMQ and HLGT combined. The number and percentage of subjects who experienced fracture events will be summarized by treatment group. A data listing of fracture events will be provided.

7.3.4. Assessment of Fracture Probability

Fracture probabilities will be assessed using FRAX®, a computer based algorithm developed by the World Health Organization (WHO; http://www.shef.ac.uk/FRAX).

The FRAX algorithm is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. The algorithm provides both the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture).

The FRAX model is constructed from real data in population-based cohorts around the world that have a limited age range. For an age below 40 or above 90 years, the tool will calculate the probability of fracture at the age of 40 or 90 years, respectively. Due to the age limitation, 2 sets of analyses of fracture probabilities will be performed.

In the first set of analysis, summaries of baseline and change from baseline in the 10-year probabilities of hip fracture, as well as major osteoporotic fracture will be presented by treatment group and visit for subjects aged between 40 and 90 years.

In the second set of analysis, the above-specified analysis will be performed to include all subjects, where subjects with an age below 40 or above 90 years will be treated as having an age of 40 or 90 years, respectively, in computing their fracture probabilities.

Data listings of fracture risk assessment questionnaire and FRAX fracture probabilities will be provided.

7.3.5. Bone Events

The PTs for bone events were defined by selecting relevant bone PTs based on MedDRA 19.1. The predefined list of PTs, included Osteoporosis/Osteopenia and Osteonecrosis SMQ, HLGT of Fractures, and HLTs relevant to bone disorders, bone metabolism, and bone procedures. These PTs were reviewed by the Gilead medical monitor before unblinding to identify appropriate bone event PTs. The number and percentage of subjects who experienced treatment-emergent bone events will be summarized by treatment group. 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 phosphorous < 2 mg/dL

Treatment-emergent confirmed renal abnormalities will be summarized for double-blind phase. All confirmed renal abnormalities including those occurred during open-label phase and 24-week treatment-free follow-up period will be listed.

7.4.2. Serum Creatinine

The baseline and change from baseline in serum creatinine at Week 48 will be summarized using descriptive statistics.

Missing values for serum creatinine will be imputed using LOCF up to Week 96 for the analyses of change from baseline in serum creatinine. The last on-treatment postbaseline observation will be carried forward to impute the missing value. Baseline observation will not be carried forward.

Change from baseline in observed serum creatinine will be analyzed similarly.

For all of the other renal safety analyses, observed creatinine values will be used.

Median (Q1, Q3) and mean (95% CI) of change from baseline in observed serum creatinine overtime will be plotted by treatment group.

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 will also be provided.

The number and proportion of subjects with decrease from baseline of ≥ 25% and ≥ 50% in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ will be summarized by treatment groups.

The number and proportion of subjects in each stage of CKD will be summarized by baseline stages of CKD for the double-blind phase up to Week 96.

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:** $eGFR_{CG}$ < 30 mL/min

Cystatin C will be collected for each subject at baseline visit (protocol amendment 2.1 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 baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ over time will be plotted.

7.4.4. Treatment-Emergent Proteinuria (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) through Week 48 will be summarized by treatment group. A listing of subjects 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. Median (Q1, Q3) percentage change from baseline over time will be plotted by treatment group.

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.

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

Median (Q1, Q3) percentage change from baseline over time will be plotted by treatment group.

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 reabsoprtion 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 $FEPO_4$ 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.

Median (Q1, Q3) change from baseline in TmP/GFR, $FEPO_4$, and FEUA over time will be plotted by treatment group. A listing of renal biomarker data will be provided.

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. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.7. Prior Hepatitis B Medications

Prior HBV medications will be summarized by treatment group. 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 from study Day 1 up to the date of last dose of blinded study drug will be summarized (number and percentage of subjects) for the double-blind phase by treatment group and WHO drug class and preferred name. Multiple drug use (by preferred name) will be counted only once per subject. 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

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

Summaries of concomitant medications will be provided for the Safety Analysis Set. Subjects with any concomitant medication use will also be listed.

7.9. Electrocardiogram (ECG) Results

The number and percentage of subjects 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.

A by-subject 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 subjects experiencing pregnancy during the study.

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

Alcohol use data will also be listed.

7.11. Changes From Protocol-Specified Safety Analyses

Treatment-emergent proteinuria was not included as a key secondary safety endpoint 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 subjects was not included as a secondary objective of this study and is added in the SAP.

8. REFERENCES

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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

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

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

FRAX® (WHO Collaborating Center for Metabolic Bone Disease, University of Sheffield, UK) is to be used for the 10-year probabilities of hip fracture or a major osteoporotic fracture.

10. SAP REVISION

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

11. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings
Appendix 2. Fracture Events
Appendix 3. Bone Events
Appendix 4. Potential Uveitis
Appendix 5. Potential Cardiovascular or Cerebrovascular Events

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table of contents of TFLs for Week 48 analysis is as follows:

Table Number	Title	Analysis Set
1	Enrollment by Region, Country, and Investigator	Safety Analysis Set
2	Enrollment by Randomization Stratum	Safety Analysis Set
3	Subject Disposition	All Screened Subjects
4	Analysis Set	Randomized Analysis Set
5	Demographics and Baseline Characteristics	Safety Analysis Set
6	Baseline Disease Characteristics	Safety Analysis Set
7	Risk Factors for HBV Infections	Safety Analysis Set
8	Prior HBV Medications	Safety Analysis Set
9	Duration of Exposure to Blinded Study Drug	Safety Analysis Set
10.1	Time to Premature Discontinuation of Blinded Study Drug (Kaplan-Meier Estimate)	Safety Analysis Set
10.2	Supporting Table for Table 11.1: Percentiles of Time to Premature Discontinuation of Blinded Study Drug	Safety Analysis Set
10.3	Supporting Table for Table 11.1: Listing of Time and Censoring Status of Premature Discontinuation of Blinded Study Drug	Safety Analysis Set
11	Adherence to Blinded Study Drug	Safety Analysis Set
12	HBV DNA Outcome at Week 48 (HBV DNA Cutoff at 29 IU/mL, Missing = Failure)	Full Analysis Set
13	HBV DNA Outcome at Week 48 (HBV DNA Cutoff at 29 IU/mL, Missing = Failure)	Week 48 PP Analysis Set
14.1	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit (Missing = Failure)	Full Analysis Set
14.2	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit (Missing = Excluded)	Full Analysis Set
15	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit (Missing = Failure)	Week 48 PP Analysis Set
16	Proportion of Subjects with HBV DNA < 29 IU/mL at Week 48 by Subgroup (Missing = Failure)	Full Analysis Set
17	HBV DNA ($\log_{10}$ IU /mL) and Change from Baseline in HBV DNA ($\log_{10}$ IU /mL) by Visit	Full Analysis Set
18.1	Proportion of Subjects with HBeAg Loss/Seroconversion by Visit (Missing = Failure)	Serologically Evaluable Full Analysis Set
18.2	Proportion of Subjects with HBeAg Loss/Seroconversion by Visit (Missing = Excluded)	Serologically Evaluable Full Analysis Set
19.1	Proportion of Subjects with HBsAg Loss/Seroconversion by Visit (Missing = Failure)	Serologically Evaluable Full Analysis Set
19.2	Proportion of Subjects with HBsAg Loss/Seroconversion by Visit (Missing = Excluded)	Serologically Evaluable Full Analysis Set

Table Number	Title	Analysis Set
20	HBsAg (log_{10} IU /mL) and Change from Baseline in HBsAg (log_{10} IU /mL) by Visit	Full Analysis Set
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21.1.2	Proportion of Subjects with Normal ALT by Visit by Central Lab Normal Range (Missing = Excluded)	Full Analysis Set
21.2.1	Proportion of Subjects with Normal ALT by Visit by AASLD Normal Range (Missing = Failure)	Full Analysis Set
21.2.2	Proportion of Subjects with Normal ALT by Visit by AASLD Normal Range (Missing = Excluded)	Full Analysis Set
22.1.1	Proportion of Subjects with ALT Normalization by Visit by Central Lab Normal Range (Missing = Failure)	Full Analysis Set with Baseline ALT > ULN
22.1.2	Proportion of Subjects with ALT Normalization by Visit by Central LabNormal Range (Missing = Excluded)	Full Analysis Set with Baseline ALT > ULN
22.2.1	Proportion of Subjects with ALT Normalization by Visit by AASLD Normal Range (Missing = Failure)	Full Analysis Set with Baseline ALT > ULN
22.2.2	Proportion of Subjects with ALT Normalization by Visit by AASLD Normal Range (Missing = Excluded)	Full Analysis Set with Baseline ALT > ULN
23	ALT (U/L) and Change from Baseline in ALT (U/L) by Visit	Full Analysis Set
24	Fibrotest Score and Change from Baseline in Fibrotest Score by Visit	Full Analysis Set
25	Shift Table of Fibrosis Stage by FibroTest® by Visit	Full Analysis Set
26	Treatment-Emergent Adverse Events: Overall Summary	Safety Analysis Set
27	Treatment-Emergent Adverse Events	Safety Analysis Set
28	Treatment-Emergent Nonserious Adverse Events Occurring in >= 5% of Subjects in Any Treatment Group	Safety Analysis Set
29	Grade 2, 3, or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
30	Grade 3 or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
31	Treatment-Emergent Study Drug-Related Adverse Events	Safety Analysis Set
32	Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Events	Safety Analysis Set
33	Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Events	Safety Analysis Set
34	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
35	Treatment-Emergent Study Drug-Related Serious Adverse Events	Safety Analysis Set
36	Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation	Safety Analysis Set
37	Treatment-Emergent Adverse Events Leading to Dose Modification or Study Drug Interruption	Safety Analysis Set
38	Treatment-Emergent Potential Uveitis Events	Safety Analysis Set
39	Treatment-Emergent Potential Cardiovascular Events	Safety Analysis Set

Table Number	Title	Analysis Set
40	Treatment-Emergent Potential Serious Cardiovascular Events	Safety Analysis Set
41	Treatment-Emergent Laboratory Abnormalities	Safety Analysis Set
42	Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
43	Treatment-Emergent Marked Laboratory Abnormalities	Safety Analysis Set
44	Treatment-Emergent ALT Elevation	Safety Analysis Set
45.1	Hematology: Summary of Hemoglobin (g/dL) by Visit	Safety Analysis Set
45.2	Hematology: Summary of Hematocrit (%) by Visit	Safety Analysis Set
45.3	Hematology: Summary of MCH (pg) by Visit	Safety Analysis Set
45.4	Hematology: Summary of MCHC (g/dL) by Visit	Safety Analysis Set
45.5	Hematology: Summary of MCV (fL) by Visit	Safety Analysis Set
45.6	Hematology: Summary of RBC (10^6/uL) by Visit	Safety Analysis Set
45.7	Hematology: Summary of Absolute Basophils (10^3/uL) by Visit	Safety Analysis Set
45.8	Hematology: Summary of Absolute Eosinophils (10^3/uL) by Visit	Safety Analysis Set
45.9	Hematology: Summary of Absolute Lymphocytes (10^3/uL) by Visit	Safety Analysis Set
45.10	Hematology: Summary of Absolute Monocytes (10^3/uL) by Visit	Safety Analysis Set
45.11	Hematology: Summary of Absolute Neutrophils (10^3/uL) by Visit	Safety Analysis Set
45.12	Hematology: Summary of Platelet Count (10^3/uL) by Visit	Safety Analysis Set
45.13	Hematology: Summary of WBC (10^3/uL) by Visit	Safety Analysis Set
46.1	Chemistry: Summary of Bicarbonate (mEq/L) by Visit	Safety Analysis Set
46.2	Chemistry: Summary of Calcium (Albumin Corrected, mg/dL) by Visit	Safety Analysis Set
46.3	Chemistry: Summary of Chloride (mEq/L) by Visit	Safety Analysis Set
46.4	Chemistry: Summary of Magnesium (mg/dL) by Visit	Safety Analysis Set
46.5	Chemistry: Summary of Phosphorus (mg/dL) by Visit	Safety Analysis Set
46.6	Chemistry: Summary of Potassium (mEq/L) by Visit	Safety Analysis Set
46.7	Chemistry: Summary of Sodium (mEq/L) by Visit	Safety Analysis Set
46.8	Chemistry: Summary of Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
46.9	Chemistry: Summary of AST (U/L) by Visit	Safety Analysis Set
46.10	Chemistry: Summary of Amylase (U/L) by Visit	Safety Analysis Set
46.11	Chemistry: Summary of Lipase (U/L) by Visit	Safety Analysis Set
46.12	Chemistry: Summary of Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
46.13	Chemistry: Summary of Direct Bilirubin (mg/dL) by Visit	Safety Analysis Set
46.14	Chemistry: Summary of Indirect Bilirubin (mg/dL) by Visit	Safety Analysis Set
46.15	Chemistry: Summary of GGT (U/L) by Visit	Safety Analysis Set

Table Number	Title	Analysis Set
46.16	Chemistry: Summary of LDH (U/L) by Visit	Safety Analysis Set
46.17	Chemistry: Summary of Blood Urea Nitrogen (BUN, mg/dL) by Visit	Safety Analysis Set
46.18	Chemistry: Summary of Uric Acid (mg/dL) by Visit	Safety Analysis Set
46.19	Chemistry: Summary of Albumin (g/dL) by Visit	Safety Analysis Set
46.20	Chemistry: Summary of Creatine Kinase (U/L) by Visit	Safety Analysis Set
46.21	Chemistry: Summary of Total Protein (g/dL) by Visit	Safety Analysis Set
47.1.1	Metabolic Assessments: Summary of Fasting Total Cholesterol (mg/dL) by Visit	Safety Analysis Set
47.1.2	Metabolic Assessments: Shift Table of Fasting Total Cholesterol (mg/dL) by Visit	Safety Analysis Set
47.2.1	Metabolic Assessments: Summary of Fasting Direct LDL (mg/dL) by Visit	Safety Analysis Set
47.2.2	Metabolic Assessments: Shift Table of Fasting Direct LDL (mg/dL) by Visit	Safety Analysis Set
47.3.1	Metabolic Assessments: Summary of Fasting HDL (mg/dL) by Visit	Safety Analysis Set
47.3.2	Metabolic Assessments: Shift Table of Fasting HDL (mg/dL) by Visit	Safety Analysis Set
47.4	Metabolic Assessments: Summary of Fasting Total Cholesterol to HDL Ratio by Visit	Safety Analysis Set
47.5.1	Metabolic Assessments: Summary of Fasting Triglycerides (mg/dL) by Visit	Safety Analysis Set
47.5.2	Metabolic Assessments: Shift Table of Fasting Triglycerides (mg/dL) by Visit	Safety Analysis Set
47.6	Metabolic Assessments: Summary of Fasting Glucose (mg/dL) by Visit	Safety Analysis Set
47.7.1	Summary of Subjects Taking Lipid Modifying Medications at Study Entry	Safety Analysis Set
47.7.2	Summary of Subjects Initiating Lipid Modifying Medications during Double-Blind Phase	Safety Analysis Set
47.8.1	Summary of Fasting Total Cholesterol (mg/dL) at Baseline and Week 48 (Excluding Subjects Taking any Lipid Modifying Medication)	Safety Analysis Set
47.8.2	Summary of Fasting Direct LDL (mg/dL) at Baseline and Week 48 (Excluding Subjects Taking any Lipid Modifying Medication)	Safety Analysis Set
47.8.3	Summary of Fasting HDL (mg/dL) at Baseline and Week 48 (Excluding Subjects Taking any Lipid Modifying Medication)	Safety Analysis Set
47.8.4	Summary of Fasting Triglycerides (mg/dL) at Baseline and Week 48 (Excluding Subjects Taking any Lipid Modifying Medication)	Safety Analysis Set

Table Number	Title	Analysis Set
47.8.5	Summary of Fasting Total Cholesterol to HDL Ratio at Baseline and Week 48 (Excluding Subjects Taking any Lipid Modifying Medication)	Safety Analysis Set
48.1.1	Percentage Change from Baseline in Hip Bone Mineral Density by Visit (LOCF Imputation)	Hip DXA Analysis Set
48.1.2	Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data)	Hip DXA Analysis Set
48.2.1	Percentage Change from Baseline in Spine Bone Mineral Density by Visit (LOCF Imputation)	Spine DXA Analysis Set
48.2.2	Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data)	Spine DXA Analysis Set
49.1	Clinical Hip Bone Mineral Density Status by Baseline Status and Visit	Hip DXA Analysis Set
49.2	Clinical Spine Bone Mineral Density Status by Baseline Status and Visit	Spine DXA Analysis Set
50.1	Gradation of the Percentage Change in Hip Bone Mineral Density by Visit	Hip DXA Analysis Set
50.2	Gradation of the Percentage Change in Spine Bone Mineral Density by Visit	Spine DXA Analysis Set
51.1	Bone Biomarkers: Summary of Serum C-type Collagen Sequence (CTX, ng/mL) by Visit	Safety Analysis Set
51.2	Bone Biomarkers: Summary of Serum Bone Procollagen Type 1 N-terminal Propeptide (P1NP, ng/mL) by Visit	Safety Analysis Set
51.3	Bone Biomarkers: Summary of Serum Parathyroid Hormone (PTH, pg/mL) by Visit	Safety Analysis Set
51.4	Bone Biomarkers: Summary of Osteocalcin (OC, ng/mL) by Visit	Safety Analysis Set
51.5	Bone Biomarkers: Summary of Bone Specific Alkaline Phosphatase (bsAP, ug/L) by Visit	Safety Analysis Set
52	Treatment-Emergent Fracture Events	Safety Analysis Set
53.1.1	Summary of 10 Year Probability of Hip Fracture (%) by Visit (Age ≥ 40 Years)	Hip DXA Analysis Set
53.1.2	Summary of 10 Year Probability of Hip Fracture (%) by Visit (All Subjects)	Hip DXA Analysis Set
53.2.1	Summary of 10 Year Probability of Major Osteoporotic Fracture (%) by Visit (Age ≥ 40 Years)	Hip DXA Analysis Set
53.2.2	Summary of 10 Year Probability of Major Osteoporotic Fracture (%) by Visit (All Subjects)	Hip DXA Analysis Set
54	Treatment-Emergent Bone Events	Safety Analysis Set
55	Treatment-Emergent Confirmed Renal Laboratory Abnormality	Safety Analysis Set
56.1	Summary of Serum Creatinine (mg/dL) by Visit (LOCF Imputation)	Safety Analysis Set
56.2	Summary of Serum Creatinine (mg/dL) by Visit (Observed Data)	Safety Analysis Set

Table Number	Title	Analysis Set
57.1	Summary of Estimated Glomerular Filtration Rate (eGFR) by Cockcroft-Gault (mL/min) by Visit	Safety Analysis Set
57.2	Summary of Estimated Glomerular Filtration Rate (eGFR) by CKD-EPI Creatinine (mL/min/1.73 m^2) by Visit	Safety Analysis Set
57.3	Summary of Subjects with Percentage Decrease from Baseline >= 25% and >= 50% in eGFR	Safety Analysis Set
57.4	Shift Table of Chronic Kidney Disease (CKD) Stage by Baseline CKD Stage	Safety Analysis Set
58	Treatment-Emergent Proteinuria by Urinalysis (Dipstick)	Safety Analysis Set
59.1	Renal Biomarkers: Summary of Urine Creatinine (mg/dL) by Visit	Safety Analysis Set
59.2	Renal Biomarkers: Summary of Urine RBP to Creatinine Ratio (ug/g) by Visit	Safety Analysis Set
59.3	Renal Biomarkers: Summary of Urine Beta-2-Microglobulin to Creatinine Ratio (ug/g) by Visit	Safety Analysis Set
59.4	Renal Biomarkers: Summary of Urine Protein to Creatinine Ratio (UPCR, mg/g) by Visit	Safety Analysis Set
59.5	Renal Biomarkers: Summary of Urine Albumin to Creatinine Ratio (UACR, mg/g) by Visit	Safety Analysis Set
60.1	Shift Table of Urine Protein to Creatinine Ratio (UPCR) Category (≤ 200 vs > 200 mg/g) by Baseline Category	Safety Analysis Set
60.2	Shift Table of Urine Albumin to Creatinine Ratio (UACR) Category (< 30 vs ≥ 30 mg/g) by Baseline Category	Safety Analysis Set
61	Summary of TmP/GFR Ratio (mg/dL) by Visit	Safety Analysis Set
62	Summary of Urine Fractional Excretion of Phosphate ($FEPO_4$, %) by Visit	Safety Analysis Set
63	Summary of Urine Fractional Excretion of Uric Acid (FEUA, %) by Visit	Safety Analysis Set
64	Summary of Body Weight (kg) by Visit	Safety Analysis Set
65	Concomitant Medications During Study by Drug Class and Generic Name	Safety Analysis Set
66	Safety ECG Results by Baseline ECG Category and Visit	Safety Analysis Set

Figure Number	Title	Analysis Set
1	Subject Disposition	All Screened Subjects
2	Time to Premature Discontinuation of Blinded Study Drug (Kaplan-Meier Estimate)	Safety Analysis Set
3.1	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit: Missing = Failure	Full Analysis Set
3.2	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit: Missing = Excluded	Full Analysis Set
4	Proportion of Subjects with HBV DNA < 29 IU/mL by Visit: Missing = Failure	Week 48 PP Analysis Set
5	Mean and 95% CIs of Change from Baseline in HBV DNA ($\log_{10}$ IU/mL) by Visit (Observed Data)	Full Analysis Set
6	Mean and 95% CIs of Change from Baseline in HBsAg ($\log_{10}$ IU/mL) by Visit (Observed Data)	Full Analysis Set
7.1	Proportion of Subjects with ALT Normalization by Visit by Central Laboratory Normal Range: Missing = Failure	Full Analysis Set
7.2	Proportion of Subjects with ALT Normalization by Visit by AASLD Normal Range: Missing = Failure	Full Analysis Set
8	Mean and 95% CIs of Change from Baseline in ALT (U/L) (Observed Data)	Full Analysis Set
9	Mean and 95% CIs of Change from Baseline in Fibrotest Score (Observed Data)	Full Analysis Set
10.1	Median (Q1, Q3) of Change from Baseline in Fasting Total Cholesterol (mg/dL) by Visit	Safety Analysis Set
10.2	Median (Q1, Q3) of Change from Baseline in Fasting Direct LDL (mg/dL) by Visit	Safety Analysis Set
10.3	Median (Q1, Q3) of Change from Baseline in Fasting HDL (mg/dL) by Visit	Safety Analysis Set
10.4	Median (Q1, Q3) of Change from Baseline in Fasting Total Cholesterol to HDL Ratio by Visit	Safety Analysis Set
10.5	Median (Q1, Q3) of Change from Baseline in Fasting Triglycerides (mg/dL) by Visit	Safety Analysis Set
10.6	Median (Q1, Q3) of Change from Baseline in Fasting Glucose (mg/dL) by Visit	Safety Analysis Set
11.1.1	Median (Q1, Q3) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data)	Hip DXA Analysis Set
11.1.2	Median (Q1, Q3) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data)	Spine DXA Analysis Set
11.2.1	Mean and 95% CIs of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data)	Hip DXA Analysis Set

Figure Number	Title	Analysis Set
11.2.2	Mean and 95% CIs of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data)	Spine DXA Analysis Set
12.1	Median (Q1, Q3) of Percentage Change from Baseline in Serum C-type Collagen Sequence (CTX) by Visit	Safety Analysis Set
12.2	Median (Q1, Q3) of Percentage Change from Baseline in Serum Bone Procollagen Type 1 N-terminal Propeptide (P1NP) by Visit	Safety Analysis Set
12.3	Median (Q1, Q3) of Percentage Change from Baseline in Serum Parathyroid Hormone (PTH) by Visit	Safety Analysis Set
12.4	Median (Q1, Q3) of Percentage Change from Baseline in Osteocalcin (OC) by Visit	Safety Analysis Set
12.5	Median (Q1, Q3) of Percentage Change from Baseline in Bone Specific Alkaline Phosphatase (bsAP) by Visit	Safety Analysis Set
13.1	Median (Q1, Q3) of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data)	Safety Analysis Set
13.2	Mean and 95% CIs of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data)	Safety Analysis Set
14.1	Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault (mL/min) by Visit	Safety Analysis Set
14.2	Median (Q1, Q3) of Change from Baseline in Estimated GFR by CKD-EPI Creatinine (mL/min/1.73 m^2) by Visit	Safety Analysis Set
15.1	Median (Q1, Q3) of Percentage Change from Baseline in Urine RBP to Creatinine Ratio by Visit	Safety Analysis Set
15.2	Median (Q1, Q3) of Percentage Change from Baseline in Urine Beta-2-Microglobulin to Creatinine Ratio by Visit	Safety Analysis Set
16.1	Median (Q1, Q3) of Percentage Change from Baseline in Urine Protein to Creatinine Ratio (UPCR) by Visit	Safety Analysis Set
16.2	Median (Q1, Q3) of Percentage Change from Baseline in Urine Albumin to Creatinine Ratio (UACR) by Visit	Safety Analysis Set
17	Median (Q1, Q3) of Change from Baseline in TmP/GFR Ratio (mg/dL) by Visit	Safety Analysis Set
18	Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Phosphate ($FEPO_4$, %) by Visit	Safety Analysis Set
19	Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Uric Acid (FEUA, %) by Visit	Safety Analysis Set

Listing Number	Title	Analysis Set
1	Subject Profiles	Randomized Analysis Set
2	Subject Disposition	Randomized Analysis Set
3.1	Subjects Who Were Excluded from Analysis Sets	Randomized Analysis Set
3.2	Subjects Who Were in the Full Analysis Set but Not in the PP Analysis Set	Full Analysis Set
4.1	Enrollment	Randomized Analysis Set
4.2	Eligibility Criteria Not Met	Randomized Analysis Set
4.3	Enrollment Summary	Subjects Not Enrolled
5.1	HBV DNA Stratification Discrepancies Between HBV DNA Stratum Entered into IWRS and Actual Screening HBV DNA Stratum	Randomized Analysis Set
5.2	HBV DNA Level Classification Difference Between Randomization Stratum by Screening and Baseline HBV DNA Level	Randomized Analysis Set
6	Subjects Who Received the Wrong Study Drug Treatment (Other Than That They Were Randomized to)	Randomized Analysis Set
7	Demographics and Baseline Characteristics	Randomized Analysis Set
8.1	Baseline Disease Characteristics (Part I)	Randomized Analysis Set
8.2	Baseline Disease Characteristics (Part II)	Randomized Analysis Set
9	Medical History	Randomized Analysis Set
10	Risk Factors for HBV Infection	Randomized Analysis Set
11	Prior HBV Medications	Randomized Analysis Set
12	Study Drug Administration	Randomized Analysis Set
13	Study Drug Accountability and Adherence	Randomized Analysis Set
14	HBV DNA	Randomized Analysis Set
15	Subjects with HBV DNA value above or at 29 IU/mL at Week 48 (or Last Visit if Prior to Week 48)	Randomized Analysis Set
16	HBV Serology	Randomized Analysis Set
17	Subjects with HBeAg Loss and/or HBeAg Seroconversion	Randomized Analysis Set: Subjects with Serologically Evaluable Data
18	Subjects with HBsAg Loss and/or HBsAg Seroconversion	Randomized Analysis Set: Subjects with Serologically Evaluable Data
19	Fibrosis Assessment by FibroTest®	Randomized Analysis Set
20	All Adverse Events	Randomized Analysis Set
21	Grade 3 and 4 Adverse Events	Randomized Analysis Set

Listing Number	Title	Analysis Set
22	Serious Adverse Events	Randomized Analysis Set
23	Study Drug-Related Serious Adverse Events	Randomized Analysis Set
24	Adverse Events Leading to Premature Study Drug Discontinuation	Randomized Analysis Set
25	Adverse Events Leading to Dose Modification or Study Drug Interruption	Randomized Analysis Set
26	Death Report	Randomized Analysis Set
27	Potential Uveitis Events	Randomized Analysis Set
28	Potential Cardiovascular Events	Randomized Analysis Set
29	Graded Laboratory Abnormalities	Randomized Analysis Set
30	Grade 3 or 4 Laboratory Abnormalities	Randomized Analysis Set
31	Laboratory Tests Related to Hepatic Function	Randomized Analysis Set
32	Hepatic Ultrasound for Hepatocellular Carcinoma (HCC) Surveillance	Randomized Analysis Set
33	ALT Elevation	Randomized Analysis Set
34.1	Clinical Laboratory Data: Hematology (Part I)	Randomized Analysis Set
34.2	Clinical Laboratory Data: Hematology (Part II)	Randomized Analysis Set
34.3	Clinical Laboratory Data: Hematology (Part III)	Randomized Analysis Set
34.4	Clinical Laboratory Data: Hematology (Part IV)	Randomized Analysis Set
35.1	Clinical Laboratory Data: Chemistry (Part I)	Randomized Analysis Set
35.2	Clinical Laboratory Data: Chemistry (Part II)	Randomized Analysis Set
35.3	Clinical Laboratory Data: Chemistry (Part III)	Randomized Analysis Set
35.4	Clinical Laboratory Data: Chemistry (Part IV)	Randomized Analysis Set
36	Metabolic Assessment: Glucose and Lipid Panel	Randomized Analysis Set
37.1	Clinical Laboratory Data: Urinalysis (Part I)	Randomized Analysis Set
37.2	Clinical Laboratory Data: Urinalysis (Part II)	Randomized Analysis Set
37.3	Clinical Laboratory Data: Urinalysis (Part III)	Randomized Analysis Set
38.1	Clinical Laboratory Data: Urine Chemistry (Part I)	Randomized Analysis Set
38.2	Clinical Laboratory Data: Urine Chemistry (Part II)	Randomized Analysis Set
39	Clinical Laboratory Data: HAV/HCV/HDV/HEV/HIV Serology	Randomized Analysis Set
40	Clinical Laboratory Data: Pregnancy Test	Randomized Analysis Set
41	Reference Ranges for Laboratory Tests	
42.1	Hip Bone Mineral Density Results	Randomized Analysis Set: Subjects with Any Hip DXA Data

Listing Number	Title	Analysis Set
42.2	Spine Bone Mineral Density Results	Randomized Analysis Set: Subjects with Any Spine DXA Data
43.1	Subjects with > 5% Decline in Hip Bone Mineral Density	Randomized Analysis Set: Subjects with Any Hip DXA Data
43.2	Subjects with > 5% Decline in Spine Bone Mineral Density	Randomized Analysis Set: Subjects with Any Spine DXA Data
44.1	Bone Biomarkers Results (Part I)	Randomized Analysis Set
44.2	Bone Biomarkers Results (Part II)	Randomized Analysis Set
45	Fracture Events	Randomized Analysis Set
46.1	FRAX 10 Year Fracture Probabilities	Randomized Analysis Set: Subjects with Any Hip DXA Data
46.2	FRAX Risk Assessment Questionnaire	Randomized Analysis Set
47	Bone Events	Randomized Analysis Set
48	Confirmed Renal Abnormalities	Randomized Analysis Set
49	Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)	Randomized Analysis Set
50	Subjects with eGFR < 50 (by CG, CKD-EPI Creatinine, or CKD-EPI Cystatin C)	Randomized Analysis Set
51	Treatment-Emergent Proteinuria	Randomized Analysis Set
52.1	Renal Biomarkers Results (Part I)	Randomized Analysis Set
52.2	Renal Biomarkers Results (Part II)	Randomized Analysis Set
53.1	Subjects with UPCR > 200 mg/g	Randomized Analysis Set
53.2	Subjects with UACR ≥ 30 mg/g	Randomized Analysis Set
54	Vital Signs	Randomized Analysis Set
55	Concomitant Medications	Randomized Analysis Set
56	12-Lead Electrocardiogram Results	Randomized Analysis Set
57	Pregnancy Report	Randomized Analysis Set
58	Cirrhosis Assessment	Randomized Analysis Set
59	Hepatocellular Carcinoma Assessment	Randomized Analysis Set
60	Alcohol Use	Randomized Analysis Set

Appendix 2. Fracture Events

The selected PTs of fracture events from SMQ of Osteoporosis/Osteopenia and HLGT of Fractures are listed as follows:

	Selected Preferred Terms	Selection Type
1	Acetabulum fracture	cSMQ+cHLGT
2	Ankle fracture	cHLGT
3	Atypical femur fracture	cSMQ+cHLGT
4	Atypical fracture	cHLGT
5	Avulsion fracture	cHLGT
6	Bone fissure	cHLGT
7	Bone fragmentation	cHLGT
8	Cervical vertebral fracture	cSMQ+cHLGT
9	Chance fracture	cHLGT
10	Clavicle fracture	cHLGT
11	Closed fracture manipulation	cSMQ
12	Comminuted fracture	cHLGT
13	Complicated fracture	cHLGT
14	Compression fracture	cHLGT
15	Craniofacial fracture	cHLGT
16	Epiphyseal fracture	cHLGT
17	External fixation of fracture	cSMQ
18	Facial bones fracture	cHLGT
19	Femoral neck fracture	cSMQ+cHLGT
20	Femur fracture	cSMQ+cHLGT
21	Fibula fracture	cHLGT
22	Flail chest	cHLGT
23	Foot fracture	cHLGT
24	Forearm fracture	cSMQ+cHLGT
25	Fracture	cSMQ+cHLGT
26	Fracture displacement	cHLGT
27	Fracture of clavicle due to birth trauma	cHLGT
28	Fracture treatment	cSMQ
29	Fractured coccyx	cHLGT
30	Fractured ischium	cSMQ+cHLGT
31	Fractured sacrum	cSMQ+cHLGT
32	Fractured skull depressed	cHLGT
33	Greenstick fracture	cHLGT
34	Hand fracture	cHLGT
35	Hip fracture	cSMQ+cHLGT
36	Humerus fracture	cHLGT

	Selected Preferred Terms	Selection Type
37	Ilium fracture	cSMQ+cHLGT
38	Impacted fracture	cHLGT
39	Internal fixation of fracture	cSMQ
40	Jaw fracture	cHLGT
41	Limb fracture	cHLGT
42	Lower limb fracture	cHLGT
43	Lumbar vertebral fracture	cSMQ+cHLGT
44	Multiple fractures	cSMQ+cHLGT
45	Open fracture	cHLGT
46	Open reduction of fracture	cSMQ
47	Open reduction of spinal fracture	cSMQ
48	Osteochondral fracture	cHLGT
49	Osteoporotic fracture	cSMQ+cHLGT
50	Patella fracture	cHLGT
51	Pathological fracture	cSMQ+cHLGT
52	Pelvic fracture	cSMQ+cHLGT
53	Periprosthetic fracture	cHLGT
54	Pubis fracture	cSMQ+cHLGT
55	Radius fracture	cSMQ+cHLGT
56	Rib fracture	cSMQ+cHLGT
57	Sacroiliac fracture	cSMQ+cHLGT
58	Scapula fracture	cHLGT
59	Scapulothoracic dissociation	cHLGT
60	Skull fracture	cHLGT
61	Skull fractured base	cHLGT
62	Spinal compression fracture	cSMQ+cHLGT
63	Spinal fracture	cSMQ+cHLGT
64	Sternal fracture	cHLGT
65	Stress fracture	cHLGT
66	Tartrate-resistant acid phosphatase decreased	cSMQ
67	Thoracic vertebral fracture	cSMQ+cHLGT
68	Tibia fracture	cHLGT
69	Torus fracture	cHLGT
70	Traumatic fracture	cHLGT
71	Ulna fracture	cHLGT
72	Upper limb fracture	cHLGT
73	Vertebroplasty	cSMQ
74	Wrist fracture	cSMQ+cHLGT
75	Vertebral body replacement	cSMQ

Appendix 3. Bone Events

The selected PTs of bone events based on MedDRA 19.1 are listed as follows:

	Selected Preferred Terms
1	Costal cartilage fracture
2	Chronic kidney disease-mineral and bone disorder
3	Astragalectomy
4	Gluteoplasty
5	Rotationplasty
6	Orthoroentgenogram
7	Atypical femur fracture
8	Carpal collapse
9	Osteonecrosis
10	Osteonecrosis of external auditory canal
11	Osteonecrosis of jaw
12	Osteoradionecrosis
13	Abscess jaw
14	Abscess oral
15	Alveolar osteitis
16	Arthrodesis
17	Biopsy bone abnormal
18	Bone abscess
19	Bone debridement
20	Bone graft
21	Bone infarction
22	Bone loss
23	Bone pain
24	Bone scan abnormal
25	Candida osteomyelitis
26	Chronic recurrent multifocal osteomyelitis
27	Dental necrosis
28	Exposed bone in jaw
29	Face and mouth X-ray abnormal
30	Groin pain

	Selected Preferred Terms
31	Hip arthroplasty
32	Hip surgery
33	Jaw lesion excision
34	Jaw operation
35	Joint arthroplasty
36	Joint prosthesis user
37	Joint resurfacing surgery
38	Maxillofacial operation
39	Oral surgery
40	Osteitis
41	Osteoarthropathy
42	Osteomyelitis
43	Osteomyelitis acute
44	Osteomyelitis bacterial
45	Osteomyelitis blastomyces
46	Osteomyelitis chronic
47	Osteomyelitis drainage
48	Osteomyelitis fungal
49	Osteomyelitis salmonella
50	Osteomyelitis viral
51	Osteotomy
52	Pain in jaw
53	Periodontal destruction
54	Primary sequestrum
55	Resorption bone increased
56	Secondary sequestrum
57	Sequestrectomy
58	Staphylococcal osteomyelitis
59	Subperiosteal abscess
60	Tertiary sequestrum
61	Tooth abscess
62	Tooth infection
63	X-ray limb abnormal

	Selected Preferred Terms
64	X-ray of pelvis and hip abnormal
65	Bone density decreased
66	Bone formation decreased
67	Bone marrow oedema syndrome
68	Osteopenia
69	Osteoporosis
70	Osteoporosis postmenopausal
71	Osteoporotic fracture
72	Senile osteoporosis
73	Acetabulum fracture
74	Body height abnormal
75	Body height below normal
76	Body height decreased
77	Bone density abnormal
78	Bone formation test abnormal
79	Bone metabolism disorder
80	Bone resorption test abnormal
81	Cervical vertebral fracture
82	Closed fracture manipulation
83	C-telopeptide increased
84	Deoxypyridinoline urine increased
85	External fixation of fracture
86	Femoral neck fracture
87	Femur fracture
88	Forearm fracture
89	Fracture
90	Fracture treatment
91	Fractured ischium
92	Fractured sacrum
93	Hip fracture
94	Ilium fracture
95	Internal fixation of fracture
96	Kyphoscoliosis

	Selected Preferred Terms
97	Kyphosis
98	Lumbar vertebral fracture
99	Multiple fractures
100	N-telopeptide urine increased
101	Open reduction of fracture
102	Open reduction of spinal fracture
103	Osteocalcin increased
104	Osteoporosis prophylaxis
105	Pathological fracture
106	Pelvic fracture
107	Post-traumatic osteoporosis
108	Pubis fracture
109	Pyridinoline urine increased
110	Radius fracture
111	Rib fracture
112	Sacroiliac fracture
113	Spinal compression fracture
114	Spinal deformity
115	Spinal fracture
116	Tartrate-resistant acid phosphatase decreased
117	Thoracic vertebral fracture
118	Vertebral body replacement
119	Vertebroplasty
120	Wrist fracture
121	Wrist surgery
122	Ankle fracture
123	Atypical fracture
124	Avulsion fracture
125	Bone fissure
126	Bone fragmentation
127	Chance fracture
128	Clavicle fracture
129	Comminuted fracture

	Selected Preferred Terms
130	Complicated fracture
131	Compression fracture
132	Craniofacial fracture
133	Epiphyseal fracture
134	Facial bones fracture
135	Fibula fracture
136	Flail chest
137	Foot fracture
138	Fracture delayed union
139	Fracture displacement
140	Fracture malunion
141	Fracture nonunion
142	Fracture of clavicle due to birth trauma
143	Fractured coccyx
144	Fractured skull depressed
145	Greenstick fracture
146	Hand fracture
147	Humerus fracture
148	Impacted fracture
149	Jaw fracture
150	Limb fracture
151	Lower limb fracture
152	Open fracture
153	Osteochondral fracture
154	Patella fracture
155	Periprosthetic fracture
156	Pseudarthrosis
157	Scapula fracture
158	Scapulothoracic dissociation
159	Skull fracture
160	Skull fractured base
161	Spinal fusion fracture
162	Sternal fracture

	Selected Preferred Terms
163	Stress fracture
164	Tibia fracture
165	Torus fracture
166	Traumatic fracture
167	Ulna fracture
168	Upper limb fracture
169	Bone formation test
170	Bone resorption test
171	C-telopeptide
172	Deoxypyridinoline urine
173	N-telopeptide
174	N-telopeptide urine
175	N-telopeptide urine abnormal
176	N-telopeptide urine decreased
177	N-telopeptide urine normal
178	Osteocalcin
179	Osteocalcin decreased
180	Osteoprotegerin
181	Osteoprotegerin decreased
182	Osteoprotegerin increased
183	Osteoprotegerin ligand
184	Osteoprotegerin ligand decreased
185	Pyridinoline urine
186	Pyridinoline urine decreased
187	Tartrate-resistant acid phosphatase
188	Aneurysmal bone cyst
189	Bone callus excessive
190	Bone contusion
191	Bone cyst
192	Bone development abnormal
193	Bone disorder
194	Bone erosion
195	Bone fistula

	Selected Preferred Terms
196	Bone formation increased
197	Bone hyperpigmentation
198	Bone lesion
199	Callus formation delayed
200	Cemento osseous dysplasia
201	Dental alveolar anomaly
202	Dental cyst
203	Enostosis
204	Erdheim-Chester disease
205	Exostosis
206	Exostosis of external ear canal
207	Exostosis of jaw
208	Extraskeletal ossification
209	Hyperphosphatasaemia
210	Hypertrophic osteoarthropathy
211	Inadequate osteointegration
212	Jaw cyst
213	Jaw disorder
214	Medial tibial stress syndrome
215	Melorheostosis
216	Osteitis condensans
217	Osteitis deformans
218	Osteorrhagia
219	Osteosclerosis
220	Osteosis
221	Periosteal haematoma
222	Periostitis
223	Periostitis hypertrophic
224	Periostosis
225	Periprosthetic osteolysis
226	Post transplant distal limb syndrome
227	Radiation osteitis
228	Skeletal injury

	Selected Preferred Terms
229	Spinal column injury
230	Spinal disorder
231	Sternal injury
232	Vertebral column mass
233	Vertebral lesion
234	Vertebral wedging
235	Bone atrophy
236	Bone decalcification
237	Brown tumour
238	Craniotabes
239	Gorham's disease
240	Hereditary hypophosphataemic rickets
241	High turnover osteopathy
242	Hungry bone syndrome
243	Hypochondroplasia
244	Hypophosphataemic rickets
245	Low turnover osteopathy
246	Oncogenic osteomalacia
247	Osteolysis
248	Osteomalacia
249	Osteoporosis circumscripta cranii
250	Rachitic rosary
251	Resorption bone decreased
252	Rickets
253	Bone marrow oedema
254	Bone swelling
255	Coccydynia
256	Eagle's syndrome
257	Metatarsalgia
258	Os trigonum syndrome
259	Pubic pain
260	Spinal pain
261	Bone cyst excision

	Selected Preferred Terms
262	Bone electrostimulation therapy
263	Bone graft removal
264	Bone lesion excision
265	Bone operation
266	Bone prosthesis insertion
267	Bone trimming
268	Cementoplasty
269	Epiphyseal surgery
270	Epiphysiodesis
271	Orthopaedic procedure
272	Ostectomy
273	Osteopathic treatment
274	Osteosynthesis
275	Removal of epiphyseal fixation
276	Removal of internal fixation
277	Calcification metastatic
278	Calciphylaxis
279	Calcium deficiency
280	Calcium intoxication
281	Calcium metabolism disorder
282	Chondrocalcinosis pyrophosphate
283	Chvostek's sign
284	Dent's disease
285	Familial hypocalciuric hypercalcaemia
286	Hypercalcaemia
287	Hypercalcaemia of malignancy
288	Hypercalcaemic nephropathy
289	Hypercalcitoninaemia
290	Hypercalciuria
291	Hypocalcaemia
292	Hypocalcaemic seizure
293	Hypocalciuria
294	Hypoparathyroidism

	Selected Preferred Terms
295	Hypoparathyroidism secondary
296	Latent tetany
297	Periarthritis calcarea
298	Primary hypoparathyroidism
299	Pseudohypercalcaemia
300	Pseudohypoparathyroidism
301	Tetany
302	Tooth demineralisation
303	Trousseau's sign
304	Williams syndrome
305	Congenital syphilitic osteochondritis
306	Epiphyseal disorder
307	Epiphyseal injury
308	Epiphyses delayed fusion
309	Epiphyses premature fusion
310	Epiphysiolysis
311	Epiphysitis
312	Fracture debridement
313	Fracture reduction
314	Fractured maxilla elevation
315	Fractured zygomatic arch elevation
316	Intramedullary rod insertion
317	Skeletal traction
318	Surgical fixation of rib fracture
319	Radial head dislocation
320	Amputation
321	Arm amputation
322	Calcanectomy
323	Finger amputation
324	Finger repair operation
325	Foot amputation
326	Foot operation
327	Hand amputation

	Selected Preferred Terms
328	Hand repair operation
329	Hip disarticulation
330	Interscapulothoracic amputation
331	Leg amputation
332	Limb amputation
333	Limb immobilisation
334	Limb operation
335	Limb reattachment surgery
336	Limb reconstructive surgery
337	Metacarpal excision
338	Metatarsal excision
339	Microsurgery to hand
340	Talipes correction
341	Toe amputation
342	Toe operation
343	Trapezectomy
344	Alveolar bone resorption
345	Dwarfism
346	Osteodystrophy
347	Renal rickets
348	Aspiration bursa
349	Aspiration bursa abnormal
350	Aspiration bursa normal
351	Aspiration joint
352	Aspiration joint abnormal
353	Aspiration joint normal
354	Biopsy abdominal wall
355	Biopsy abdominal wall abnormal
356	Biopsy abdominal wall normal
357	Biopsy bone
358	Biopsy bone normal
359	Biopsy cartilage
360	Biopsy cartilage abnormal

	Selected Preferred Terms
361	Biopsy cartilage normal
362	Biopsy chest wall
363	Biopsy chest wall abnormal
364	Biopsy chest wall normal
365	Biopsy ligament
366	Biopsy ligament abnormal
367	Biopsy ligament normal
368	Biopsy muscle
369	Biopsy muscle abnormal
370	Biopsy muscle normal
371	Biopsy soft tissue
372	Biopsy tendon
373	Biopsy tendon abnormal
374	Biopsy tendon normal
375	Intervertebral disc biopsy
376	Synovial biopsy
377	Synovial biopsy abnormal
378	Synovial fluid cell count
379	Synovial fluid crystal
380	Synovial fluid crystal present
381	Synovial fluid red blood cells
382	Synovial fluid red blood cells positive
383	Synovial fluid white blood cells
384	Synovial fluid white blood cells positive
385	Arthrogram
386	Arthrogram abnormal
387	Arthrogram normal
388	Arthroscopy
389	Arthroscopy abnormal
390	Arthroscopy normal
391	Bone densitometry
392	Bone density increased
393	Bone scan

	Selected Preferred Terms
394	Bone scan normal
395	Discogram
396	Discogram abnormal
397	Discogram normal
398	Face and mouth X-ray
399	Face and mouth X-ray normal
400	Skeletal survey
401	Skeletal survey abnormal
402	Skeletal survey normal
403	Skull X-ray
404	Skull X-ray abnormal
405	Skull X-ray normal
406	Spinal X-ray
407	Spinal X-ray abnormal
408	Spinal X-ray normal
409	Ultrasound joint
410	X-ray limb
411	X-ray limb normal
412	X-ray of pelvis and hip
413	X-ray of pelvis and hip normal
414	Acute phosphate nephropathy
415	Hyperphosphataemia
416	Hyperphosphaturia
417	Hypophosphataemia
418	Phosphorus metabolism disorder
419	Pseudohyperphosphataemia
420	Dislocation of vertebra
421	Intervertebral disc injury
422	Ankle arthroplasty
423	Ankle operation
424	Arthrectomy
425	Arthrolysis
426	Arthroscopic surgery

	Selected Preferred Terms
427	Arthrotomy
428	Baker's cyst excision
429	Bone groove deepening
430	Bunion operation
431	Capsulorrhaphy
432	Delayed spinal fusion
433	Elbow operation
434	Incomplete spinal fusion
435	Knee arthroplasty
436	Knee operation
437	Ligament operation
438	Maxillonasal dysplasia
439	Meniscus operation
440	Meniscus removal
441	Patella replacement
442	Patellectomy
443	Radiolucency around implant
444	Radiotherapy to joint
445	Removal of foreign body from joint
446	Rheumatoid nodule removal
447	Rotator cuff repair
448	Shoulder arthroplasty
449	Shoulder operation
450	Synovectomy
451	Synoviorthesis
452	Temporomandibular joint surgery
453	Tophus removal operation

Appendix 4. Potential Uveitis

The selected PTs of potential uveitis from SOC of Eye Disorders are listed as follows:

	Selected Preferred Terms
1	Homonymous diplopia
2	Keratic precipitates
3	Retinal thickening
4	Vitreous haze
5	Acute zonal occult outer retinopathy
6	Anterior chamber cell
7	Anterior chamber fibrin
8	Anterior chamber flare
9	Anterior chamber inflammation
10	Aqueous fibrin
11	Autoimmune retinopathy
12	Autoimmune uveitis
13	Behcet's syndrome
14	Birdshot chorioretinopathy
15	Blau syndrome
16	Blindness
17	Blindness transient
18	Blindness unilateral
19	Chemical iritis
20	Chorioretinitis
21	Chorioretinopathy
22	Choroiditis
23	Ciliary hyperaemia
24	Cogan's syndrome
25	Cyclitic membrane
26	Cyclitis
27	Cystoid macular oedema
28	Cytomegalovirus chorioretinitis
29	Eales' disease
30	Endophthalmitis

	Selected Preferred Terms
31	Exudative retinopathy
32	Eye inflammation
33	Fuchs' syndrome
34	Glaucomatocyclitic crises
35	Hypopyon
36	Hypotony of eye
37	IRVAN syndrome
38	Infectious iridocyclitis
39	Iridocyclitis
40	Iritis
41	Koeppe nodules
42	Macular oedema
43	Necrotising retinitis
44	Non-infectious endophthalmitis
45	Noninfective chorioretinitis
46	Noninfective retinitis
47	Ocular lymphoma
48	Ocular sarcoidosis
49	Ocular toxicity
50	Ocular vasculitis
51	Optic discs blurred
52	Panophthalmitis
53	Photophobia
54	Photopsia
55	Retinal exudates
56	Retinal oedema
57	Retinal perivascular sheathing
58	Retinal pigment epitheliopathy
59	Retinal toxicity
60	Retinal vasculitis
61	Retinitis
62	Subretinal fluid
63	Sudden visual loss

	Selected Preferred Terms
64	Susac's syndrome
65	Sympathetic ophthalmia
66	Traumatic iritis
67	Tubulointerstitial nephritis and uveitis syndrome
68	Uveitic glaucoma
69	Uveitis
70	Uveitis-glaucoma-hyphaema syndrome
71	Vision blurred
72	Visual acuity reduced
73	Visual acuity reduced transiently
74	Visual field defect
75	Visual impairment
76	Vitreal cells
77	Vitreous fibrin
78	Vitreous floaters
79	Vitreous opacities
80	Vitritis
81	Vogt-Koyanagi-Harada syndrome

Appendix 5. Potential Cardiovascular or Cerebrovascular Events

	Selected Preferred Terms
1	Amaurosis fugax
2	Basal ganglia infarction
3	Basal ganglia stroke
4	Basilar artery occlusion
5	Basilar artery stenosis
6	Basilar artery thrombosis
7	Brachiocephalic arteriosclerosis
8	Brachiocephalic artery occlusion
9	Brachiocephalic artery stenosis
10	Brain hypoxia
11	Brain stem embolism
12	Brain stem infarction
13	Brain stem ischaemia
14	Brain stem stroke
15	Brain stem thrombosis
16	Capsular warning syndrome
17	Carotid angioplasty
18	Carotid arterial embolus
19	Carotid arteriosclerosis
20	Carotid artery bypass
21	Carotid artery calcification
22	Carotid artery disease
23	Carotid artery insufficiency
24	Carotid artery occlusion
25	Carotid artery restenosis
26	Carotid artery stenosis
27	Carotid artery stent insertion
28	Carotid artery stent removal
29	Carotid artery thrombosis
30	Carotid endarterectomy
31	Carotid revascularisation
32	Cerebellar artery occlusion

	Selected Preferred Terms
33	Cerebellar artery thrombosis
34	Cerebellar embolism
35	Cerebellar infarction
36	Cerebellar ischaemia
37	Cerebral arteriosclerosis
38	Cerebral artery embolism
39	Cerebral artery occlusion
40	Cerebral artery restenosis
41	Cerebral artery stenosis
42	Cerebral artery thrombosis
43	Cerebral gas embolism
44	Cerebral infarction
45	Cerebral infarction foetal
46	Cerebral ischaemia
47	Cerebral microembolism
48	Cerebral revascularisation
49	Cerebral septic infarct
50	Cerebral small vessel ischaemic disease
51	Cerebral thrombosis
52	Cerebral vascular occlusion
53	Cerebral vasoconstriction
54	Cerebral venous thrombosis
55	Cerebrovascular accident
56	Cerebrovascular disorder
57	Cerebrovascular insufficiency
58	Cerebrovascular stenosis
59	Delayed ischaemic neurological deficit
60	Embolic cerebral infarction
61	Embolic stroke
62	Hypoxic-ischaemic encephalopathy
63	Inner ear infarction
64	Ischaemic cerebral infarction
65	Ischaemic stroke

	Selected Preferred Terms
66	Lacunar infarction
67	Lacunar stroke
68	Lateral medullary syndrome
69	Migrainous infarction
70	Millard-Gubler syndrome
71	Moyamoya disease
72	Perinatal stroke
73	Post cardiac arrest syndrome
74	Post procedural stroke
75	Precerebral arteriosclerosis
76	Precerebral artery occlusion
77	Reversible cerebral vasoconstriction syndrome
78	Reversible ischaemic neurological deficit
79	Spinal artery embolism
80	Spinal artery thrombosis
81	Stroke in evolution
82	Subclavian steal syndrome
83	Thalamic infarction
84	Thrombotic cerebral infarction
85	Thrombotic stroke
86	Transient ischaemic attack
87	Vascular encephalopathy
88	Vascular stent occlusion
89	Vascular stent restenosis
90	Vascular stent stenosis
91	Vertebral artery occlusion
92	Vertebral artery stenosis
93	Vertebral artery thrombosis
94	Vertebrobasilar insufficiency
95	Angina pectoris
96	Angina unstable
97	Anginal equivalent
98	Arteriosclerosis coronary artery

	Selected Preferred Terms
99	Arteriospasm coronary
100	Coronary angioplasty
101	Coronary arterial stent insertion
102	Coronary artery bypass
103	Coronary artery disease
104	Coronary artery dissection
105	Coronary artery insufficiency
106	Coronary artery restenosis
107	Coronary artery stenosis
108	Coronary brachytherapy
109	Coronary bypass stenosis
110	Coronary endarterectomy
111	Coronary no-reflow phenomenon
112	Coronary ostial stenosis
113	Coronary revascularisation
114	Coronary vascular graft stenosis
115	Dissecting coronary artery aneurysm
116	ECG signs of myocardial ischaemia
117	External counterpulsation
118	Haemorrhage coronary artery
119	Ischaemic cardiomyopathy
120	Ischaemic mitral regurgitation
121	Microvascular coronary artery disease
122	Myocardial ischaemia
123	Percutaneous coronary intervention
124	Prinzmetal angina
125	Stress cardiomyopathy
126	Subclavian coronary steal syndrome
127	Subendocardial ischaemia
128	Arteriogram coronary abnormal
129	Cardiac stress test abnormal
130	Cardiopulmonary exercise test abnormal
131	Computerised tomogram coronary artery abnormal

	Selected Preferred Terms
132	Electrocardiogram ST segment depression
133	Electrocardiogram ST-T segment abnormal
134	Electrocardiogram ST-T segment depression
135	Electrocardiogram T wave abnormal
136	Electrocardiogram T wave inversion
137	Exercise electrocardiogram abnormal
138	Exercise test abnormal
139	Post angioplasty restenosis
140	Stress echocardiogram abnormal
141	Vascular stent restenosis
142	Vascular stent stenosis
143	Acute coronary syndrome
144	Acute myocardial infarction
145	Angina unstable
146	Blood creatine phosphokinase MB abnormal
147	Blood creatine phosphokinase MB increased
148	Coronary artery embolism
149	Coronary artery occlusion
150	Coronary artery reocclusion
151	Coronary artery thrombosis
152	Coronary bypass thrombosis
153	Coronary vascular graft occlusion
154	Kounis syndrome
155	Myocardial infarction
156	Myocardial necrosis
157	Myocardial reperfusion injury
158	Myocardial stunning
159	Papillary muscle infarction
160	Post procedural myocardial infarction
161	Postinfarction angina
162	Silent myocardial infarction
163	Troponin I increased
164	Troponin increased

	Selected Preferred Terms
165	Troponin T increased
166	Blood creatine phosphokinase abnormal
167	Blood creatine phosphokinase increased
168	Cardiac ventricular scarring
169	ECG electrically inactive area
170	ECG signs of myocardial infarction
171	Electrocardiogram Q wave abnormal
172	Electrocardiogram ST segment abnormal
173	Electrocardiogram ST segment elevation
174	Electrocardiogram ST-T segment elevation
175	Infarction
176	Myocardial necrosis marker increased
177	Scan myocardial perfusion abnormal
178	Vascular graft occlusion
179	Vascular stent occlusion
180	Vascular stent thrombosis