STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant
Name of Test Drug:	Tenofovir Alafenamide (TAF)
Study Number:	GS-US-320-3912
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase (SGPT)
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
CLCr	creatinine clearance
CMH	Cochran-Mantel-Haenszel
Cr EDTA	Chronium ethylenediamine tetraacetic acid
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
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
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
LLOQ	lower limit of quantitation
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
OAV	Oral antiviral
OC	osteocalcin
P1NP	procollagen type 1 N-terminal propeptide
PP	per protocol
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFFU	Treatment Free Follow-Up
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
TmP	tubular maximum reabsorption rate of phosphate
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the final analysis of Study GS-US-320-3912. This SAP is based on the study protocol Amendment 3.0 dated 18 June 2019 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of TAF 25 mg once daily (QD) versus TDF-containing regimens as determined by the change from baseline in estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration formula ($eGFR_{CKD-EPI}$) at Week 24
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 24

The secondary objectives of this study are as follows:

- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in serum creatinine at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 48
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 48

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1.2. Study Design

This is a randomized, open-label, single center Phase 2 study to evaluate the safety and efficacy of TAF 25 mg QD versus TDF in adult chronic hepatitis B (CHB) infection subjects with Stage 2 or greater chronic kidney disease and have previously received a liver transplant.

Treatment Groups

Approximately 50 subjects will to be randomized 1:1 to either continue current treatment regimen with TDF (alone or in combination with other approved antivirals) or to receive TAF 25 mg orally daily. Approximately 40 of 50 subjects were to be enrolled with $eGFR_{CKD-EPI}$ < 60 ml/min/1.73m^2. Randomization was stratified by screening renal function ($eGFR_{CKD-EPI}$ < 50 ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2)

- **Treatment Arm A:** approximately 25 subjects administered TAF 25 mg oral daily
- **Treatment Arm B:** approximately 25 subjects to continue administration of TDF alone or in combination with other approved antivirals as per local practice

Key Eligibility Criteria

Subjects were to have met the following key eligibility criteria:

- Documented evidence of chronic HBV infection prior to transplantation
- Primary or secondary (re-transplant), liver alone or liver and kidney transplant recipient from deceased or living donor
- Liver Transplant ≥ 12 weeks prior to screening
- Maintained on TDF alone or in combination with other approved antivirals for HBV prophylaxis or treatment
- Have been on approved HBV oral antiviral (OAV) treatment for at least 12 weeks post-transplant prior to screening, with HBV DNA < lower limit of quantitation (LLOQ) at screening
- Screening $eGFR_{CKD-EPI}$ < 90 ml/min/1.73m^2

Study Periods/Phases

The duration of the study treatment is 48 weeks with an initial screening period of 45 days. Subsequent to Screening, subjects will be randomized to receive TAF or TDF alone or in combination with approved antivirals per local practice.

CCI [redacted] If subjects CCI [redacted] choose to not continue or discontinue TAF prematurely, they will be followed for 24 weeks after the discontinuation of study treatment (ie, Treatment Free Follow-Up, TFFU) or until an alternative CHB treatment is started, whichever occurs first. In this SAP, the first 48 weeks of study treatment is referred to as randomized phase, CCI [redacted]

Schedule of Assessments

Laboratory analyses (serum chemistry, liver tests, hematology, plasma HBV DNA levels, pregnancy testing [for females of childbearing potential]), body weight, vital signs, adverse events (AEs), and concomitant medications will be performed at screening, baseline, Week 4, 8, 12, 20, 24, CCI [redacted]

HBV serology (qualitative HBsAg and HBeAg) will be performed at screening, baseline, Weeks 24, 48, CCI [redacted] and ED. HBeAb and HBsAb testing will be performed as reflex testing as needed. Bone and renal biomarker testing will be performed at baseline and then at defined intervals throughout the study. Vitamin D assessments, FibroTest® and fasting metabolic assessments (fasting glucose and lipid panel) will be performed at baseline, Weeks 24, 48, CCI [redacted] ED visit. Chronium ethylenediamine tetraacetic acid (Cr EDTA) renal scan will be performed at baseline, Week 48 CCI [redacted] visit.

Complete physical examinations will be performed at screening, baseline, and Weeks 12, 24, 48, CCI [redacted] /ED visit. Symptom directed physical examinations including body weight assessment will be conducted at all other visits. Dual energy x-ray absorptiometry (DXA) scans of the hip and spine should be performed during Screening and should be completed at least 14 days prior to the first dose of study drug, and will be conducted at Weeks 24, 48, CCI [redacted] and the ED visit if not done within the last 24 weeks of this visit. Plasma, serum, and urine will be collected at baseline and at every visit thereafter for storage.

Treatment Free Follow-Up (TFFU) 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. CCI [redacted]

Randomization

Subjects who meet eligibility criteria will be randomized 1:1 to receive TAF or either continue on TDF alone or in combination with other approved antivirals for 48 weeks. Randomization was stratified by screening renal function ($eGFR_{CKD-EPI}$ < 50 ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2)

1.3. Sample Size and Power

This is an exploratory study. No formal sample size calculation was performed.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

The data monitoring committee (DMC) reviewed the progress of the study and performed review of safety data after 30 subjects had completed 12 weeks of treatment. The DMC noted no safety concerns that would merit altering the course of the study and recommended that the study should proceed as planned.

The DMC's specific activities were defined by a mutually agreed charter, which defined the DMC's membership, conduct and meeting schedule. More details are documented in the independent DMC charter.

2.1.2. Week 24 Analysis (Primary Analysis)

The Week 24 analysis was conducted after the last subject completed the Week 24 visit or prematurely discontinued study drug. This analysis was described in the Week 24 Analysis SAP dated 19 March 2018. This is considered the primary analysis of the study. All analyses except PK analyses will be reproduced in the Final Analysis.

2.1.3. Week 48 Analysis

The Week 48 analysis was conducted after the last subject completed the randomized phase at Week 48 visit or prematurely discontinued study drug. This was an interim analysis performed based on a data snapshot.

2.1.4. Final Analysis

The final statistical analysis for the study will be conducted after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. This SAP describes the analysis plan for the Final Analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. Randomized Analysis Set

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

3.1.2. Full Analysis Set (FAS)

The FAS will include 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. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set will include all subjects who have received at least 1 dose of study drug. Subjects will be analyzed according to the treatment they actually received during the randomized phase. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. This is the primary analysis set for safety analyses.

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[redacted]

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

The Serologically Evaluable Full Analysis Set for HBsAg loss/seroconversion will include all subjects who were randomized and had received at least 1 dose of study drug, and with serology data showing the subject to be HBsAg positive and HBsAb negative or missing at baseline. Subjects will be analyzed according to the treatment to which they were randomized.

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

The Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion will include all subjects who were randomized and had received at least 1 dose of study drug, and with serology data showing the subject to be HBeAg positive and HBeAb negative or missing at baseline. Subjects will be analyzed according to the treatment to which they were randomized.

3.1.7. DXA Analysis Set

3.1.7.1. Hip DXA Analysis Set

The Hip DXA Analysis Set will include 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 randomized phase.

3.1.7.2. 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 randomized phase.

3.2. Subject Grouping

For efficacy analysis, subjects will be analyzed by randomized treatment. For safety analysis using the Safety Analysis Set, subjects will be analyzed by actual treatment received during the randomized phase.

Subjects will be grouped into the following treatment groups:

Randomized phase summaries:

- TAF 25 mg
- TDF-containing regimens

CCI [redacted]

3.3. Strata and Covariates

Subjects were to be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification was based on the following variables:

- Screening renal function ($eGFR_{CKD\text{-}EPI}$ < 50 mL/min/1.73m^2 and ≥ 50 mL/min/1.73m^2)

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety analysis.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed, unless methods for handling missing data are specified. Exceptions are presented in this document.

A missing baseline laboratory result will be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

Both baseline and postbaseline borderline results for HBeAg, hepatitis B e antibody (HBeAb), HBsAg, and hepatitis B surface antibody (HBsAb) will be imputed as follows:

- HBsAb/HBeAb borderline → HBsAb/HBeAb negative
- HBsAg/HBeAg borderline → HBsAg/HBeAg positive

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior and concomitant medications in Section 7.7.

3.5.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the analyses.

3.6. Data Handling Conventions and Transformations

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

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

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

- A value that is 1 unit less than the lower LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (x is considered as the lower LOQ). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.
- A value that is 1 unit above the upper LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (x is considered as the upper LOQ). Values with decimal points will follow the same logic as stated above.
- The lower or upper LOQ 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 lower or upper LOQ, respectively).

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 (AMPLIPREP TAQM) is above the upper limit of quantification, the corresponding diluted value (AMPLIPREP TAQ), if available, will be used.

3.7. Analysis Visit Windows

3.7.1. Definition of Study Day

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

Since the TDF group subjects are to continue administration of TDF alone or in combination with other approved antivirals as per local practice, for the TDF group the Study Day 1 is defined as: the first actual dose date on or after the latest lab or PK visit date with Baseline/Day 1 visit.

CCI [redacted]

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).

CCI [redacted]

Follow-up days are for visits occurring during the 24-week treatment-free follow-up period and calculated as (visit date – last dose date).

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

For subjects who prematurely discontinued randomized study drug or who completed randomized study drug CCI [redacted] the **Last Dose Date** is the same as Last Dose Date of Randomized Study Drug.

CCI [redacted]

Last Study Date is the latest of non-missing study drug (randomized CCI phase) start dates and end dates, the clinic visit, the laboratory visit and DXA 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 for the randomized phase (except DXA BMD) is defined as the last non-missing value obtained on or prior to Study Day 1. For DXA BMD, the baseline value is defined as the last non-missing value on or prior to Study Day 14.

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3.7.2. Analysis Visit 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 3-1 to Table 3-5) apply to baseline and on-treatment assessments only. For summaries and analysis, assessments will first be categorized into baseline and on-treatment assessments occurring during the randomized CCI phase, before applying analysis windows.

For subjects who prematurely discontinued the randomized study drug CCI , laboratory assessments up to and including the last dose date of the randomized study drug + 3 days, and DXA assessments up to and including the last dose date of the randomized study drug + 14 days, will be considered as baseline or on-treatment during the randomized phase.

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For subjects who have not discontinued the randomized study drug permanently, data collected up to database finalization date will be considered as baseline or on-treatment of the randomized phase.

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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 3-1 and Table 3-3).

The analysis windows for HBV DNA, hematology, serum chemistry and liver function tests, eGFR (by CG and 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 (FEPO4), fractional excretion of uric acid (FEUA), non-fasting glucose, weight, and vital sign assessments are provided in Table 3-1.

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

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	69
Week 12	84	70	111
Week 20	140	112	153
Week 24	168	154	209
Week 36	252	210	293
Week 48	336	294	377 (419[b])

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b Applies to UACR, UPCR, TmP/GFR, FEPO4 and FEUA only.

The analysis window for Fasting Glucose, Serum Cystatin C and eGFR by CKD-EPI Cystatin C is in Table 3-2.

Table 3-2. Analysis Visit Windows for Fasting Glucose, Serum Cystatin C and eGFR by CKD-EPI Cystatin C

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

Table 3-3. Analysis Visit Windows for BMD Results from DXA, Fibrotest, Lipid Panel and HBV Serology

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1(14[a])
Week 24	168	2(15[a])	251
Week 48	336	252	503
CCI			

a Applies to DXA only. Upper limit for baseline DXA BMD is Day 14 and lower limit for Week 24 DXA BMD is Day 15.

The analysis windows for Cr EDTA renal scan are presented in Table 3-4.

Table 3-4. Analysis Visit Windows for Cr EDTA Renal Scan

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	503
CCI			

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

Table 3-5. Analysis Visit Windows for Renal and Bone Biomarkers

Nominal Visit	Nominal Study 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
CCI			

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 3-6.

Table 3-6. Analysis Visit Windows for Post Treatment Assessments

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

3.7.3. Selection of Data in the Event of Multiple Records for an Analysis Visit Day

Depending on the statistical analysis method, single values are required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window. When a single value is needed, the following rule(s) will be used.

For baseline of the randomized phase, 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. 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:

- Alanine aminotransferase (**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):** 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 and Disposition

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

The number and percentage of subjects enrolled in each randomization stratum will be summarized based on interactive voice response system/web response system (IXRS) data. If there are discrepancies between IXRS and screening laboratory data with regard to stratum assignment, a listing of the discrepancies will be provided.

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[CCI [redacted].

Study Drug Completion

- Prematurely discontinued randomized study treatment (with summary of reasons for discontinuing treatment)
- Completed randomized study treatment
- [CCI [redacted]
- [redacted]
- [redacted]

Study Completion

- Entered 24-week treatment-free follow-up period
- Prematurely discontinued study (with summary of reasons for discontinuing study)
- Completed protocol-planned duration of the study

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

4.2. Extent of Study Drug Exposure and Adherence

Exposure data described below will be summarized for the randomized phase CCI [redacted]

4.2.1. Duration of Exposure to Randomized Study Drug

Duration of exposure to randomized study drug will be defined as (last dose date of randomized study drug – first dose date of randomized 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 randomized study drug, the latest of randomized study drug start and end dates, and the clinic and laboratory visit dates (excluding the CCI [redacted] treatment-free follow-up visit dates) will be used to impute the last dose date of randomized study drug for calculating the duration of randomized study drug exposure.

Duration of exposure to randomized study drug will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), etc.

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

4.2.2. Adherence to Randomized Study Drug

Study drug regimen adherence will be computed based on tablet counts for the TAF group only. 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 for the entire randomized dosing period up to the date of permanent discontinuation of the randomized study drug for subjects who prematurely discontinued randomized study drug or completed randomized study drug or using all data available for subjects remaining on randomized study drug.

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, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

CCI [redacted]

CCI [redacted]

4.3. 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.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason will be summarized by treatment group for the Randomized Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviations.

4.4. Assessment of COVID-19 Impact

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

4.4.1. Protocol Deviations Due to COVID-19

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

4.4.2. Missed and Virtual Visits due to COVID-19

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall, using descriptive statistics (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. A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- 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 (IU/mL)
- HBV DNA categories (< 20 IU/mL, ≥ 20 to < 69 IU/mL, ≥ 69 IU/mL)
- ALT (U/L)
- ALT level based on central laboratory normal range (≤ upper limit of normal [ULN], > ULN - 5 × ULN, > 5 × ULN – 10 × ULN, > 10 ULN)
- ALT level based on 2018 American Association for the Study of Liver Diseases (AASLD) normal range with the ULN as 25 U/L for female and 35 U/L for male (≤ ULN, > ULN − 5 × ULN, > 5 × ULN − 10 × ULN, > 10 ULN)
- Estimated GFR by CG (mL/min), CKD-EPI creatinine (mL/min/1.73 m^2), CKD-EPI Cystatin C (mL/min/1.73 m^2) and Cr EDTA (mL/min/1.73 m^2) methods
- Chronic kidney disease (CKD) stage by estimated GFR by CG, CKD-EPI creatinine, CKD-EPI Cystatin C and Cr EDTA methods
- HBeAg status (positive, negative)
- HBeAb status (positive, negative)
- HBsAg status (positive, negative)
- HBsAb status (positive, negative)

- Previous TDF use experience (yes, no) and TDF use at Day 1
- Previous Lamivudine use experience (yes, no) and Lamivudine use at Day 1
- Years positive for HBV
- Years of liver transplant
- Fibrotest score
- Fibrosis stage by fibrotest score (0 - 0.48, 0.49 - 0.74, 0.75 - 1)
- Proteinuria by urinalysis (dipstick) (Grade 0, Grade 1, Grade 2, Grade 3)
- Vitamin D
- Clinical BMD status (normal, osteopenia, osteoporosis)
- Hip fracture and major osteoporotic fracture probabilities estimated using FRAX® (see Section 7.3.4)

The stages of CKD by estimated GFR are defined as follows:

- **Stage 1:** ≥ 90
- **Stage 2:** ≥ 60 and < 90
- **Stage 3:** ≥ 30 and < 60
  - **Stage 3a:** ≥ 45 and < 60
  - **Stage 3b:** ≥ 30 and < 45
- **Stage 4:** ≥ 15 and < 30
- **Stage 5:** < 15

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The analysis of the primary efficacy endpoint was performed previously; this analysis will also be repeated in the Final Analysis for completeness.

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HBV DNA < 20 IU/mL at Week 24.

6.1.2. Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will be conducted after the last randomized subject reaches Week 24 or discontinues study drug prematurely. A Missing = Failure (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 ≥ 20 IU/mL).

6.1.3. Secondary Analysis of the Primary Efficacy Endpoint

Sensitivity analyses will be performed for the primary endpoint using Missing = Excluded (M = E) approach. 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).

6.2. Other Efficacy Endpoints

The analysis of the secondary and other efficacy endpoints at Weeks 24 and 48 was performed previously; the analysis will also be repeated in the Final Analysis for completeness.

6.2.1. Definition of Secondary and Other Efficacy Endpoints

The secondary efficacy endpoint is:

- The proportion of subjects with plasma HBV DNA < 20 IU/mL at Weeks 48

Other efficacy endpoints include:

- The proportion of subjects with normal ALT (by central laboratory and AASLD criteria) at Weeks 24 and 48
- The proportion of subjects with ALT normalization (by central laboratory and AASLD criteria) at Weeks 24 and 48

- The change from baseline in ALT at Weeks 24 and 48

[redacted]

ALT normalization is defined as ALT > ULN (by central laboratory normal range or 2018 AASLD normal range) at baseline but within normal range at a postbaseline visit

6.2.2. Analysis Methods for Secondary and Other Efficacy Endpoints

All the secondary and other 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.

In addition, the proportion of subjects with HBV DNA < 20 IU/mL and the proportion of subjects with normal ALT (by central laboratory and AASLD criteria, M = F) will be separately plotted with 95% CI over time for FAS. Median (Q1, Q3) and mean (95% CI) of change from baseline in ALT (U/L) will also be plotted over time using observed data for FAS.

6.3. Changes from Protocol-Specified Efficacy Analyses

Change from baseline in ALT was added in the SAP as other efficacy endpoints to fully explore the treatment effect of TAF versus TDF. Proportion of normal ALT and ALT normalization by visit evaluated using central laboratory and 2018 AASLD ULN were also added.

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

7. SAFETY ANALYSES

For the final safety analysis, exposure and cumulative safety data (treatment-emergent AEs, treatment-emergent laboratory abnormalities, etc) will be summarized for the randomized phase based on the Safety Analysis Set, CCI [redacted]

By-visit summary tables will be presented for the entire study treatment period (randomized CCI [redacted]), based on subjects in the Safety Analysis, starting from the randomized phase baseline.

CCI [redacted]

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

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 Adverse Events 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 Adverse Events

Serious adverse events (SAEs) are those identified as serious in the eCRF, where 'Yes' was marked for 'AE serious'. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

Summaries of treatment-emergent AEs will be provided for randomized CCI [redacted]

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

- Any AE with onset date on or after the randomized study drug start date and no later than the minimum of the randomized study drug stop date + 3 days CCI [redacted], for those who discontinued randomized study drug permanently, or
- Any AE with onset date on or after the randomized study drug start date for those who are still on the randomized study drug, or
- Any AE leading to randomized study drug discontinuation.

CCI [redacted]

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 randomized phase CCI [redacted]:

Events with Missing Onset Day and/or Month

The event is treatment-emergent during the randomized 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 randomized study drug, and

- For those who discontinued the randomized 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 minimum of the randomized study drug stop date + 3 days CCI [redacted] and

- AE End date is as follows:

  — The (complete) end date is on or after the first dose date of the randomized 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 randomized study drug, or

  — End date is completely missing

CCI [redacted]

Events with Completely Missing Onset Date

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

- The (complete) end date is on or after the first dose date of the randomized 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 randomized study drug, or

- End date is completely missing

CCI [redacted]

7.1.7. Summaries of Adverse Events 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 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 during the randomized phase refers to death that occurs between the first dose date of the randomized study drug and the minimum of the last dose date of the randomized study drug + 3 days CCI [redacted] for those who discontinued randomized study drug permanently. CCI [redacted]

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 for the randomized phase CCI [redacted] as follows:

- All treatment-emergent AEs summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent AEs
- Any Grade 2, 3, or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AE summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs

- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs leading to premature discontinuation from study drug
- All treatment-emergent AEs leading to dose modification or study drug interruption

Multiple events will be counted once only per 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

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the entire study period based on Safety Analysis. Analysis will be based on values reported in conventional units. No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for each laboratory test during the entire study period specified in the study protocol as follows:

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

7.2.1.1. Metabolic Assessments

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

Fasting lipid data (including total cholesterol, LDL, HDL and triglycerides) will also be analyzed using the following 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.

7.2.1.2. Calcium Correlated for Albumin

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

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

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

7.2.2. Graded Laboratory Values

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

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities occurring in the randomized phase are defined as values that increase by at least 1 toxicity grade from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days CCI [redacted], for those who discontinued randomized 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 randomized study drug. If the relevant baseline laboratory data are missing, any laboratory abnormality of at least Grade 1 will be considered treatment-emergent.

CCI [redacted]

Fasting glucose and nonfasting glucose are graded based on different grading scales. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose and nonfasting glucose separately.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities occurring in the randomized phase are defined as values that worsen by at least 3 grades from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days CCI [redacted], for those who discontinued randomized study drug prematurely, or values that worsen by at least 3 grades from baseline at any postbaseline visit for those who are still on randomized 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.

CCI [redacted]

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

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) for the randomized phase CCI [redacted]:

- 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 non-missing 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 randomized phase CCI [redacted]. CCI [redacted] All treatment-emergent and nontreatment-emergent ALT elevations will be included in a listing.

If the first of 2 consecutive results is in the randomized phase and the second is out of the randomized phase (ie, in the CCI [redacted] TFFU phase), then the result will be considered to be confirmed in the randomized phase (assuming both values meet the criterion). And if the criterion is met by the last value in the randomized phase and no assessments are available after due to the subject exiting the study or data not yet available, then the result will also be considered to be confirmed.

7.2.4. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 ULN; (b) > 5 x ULN
- ALT: (a) > 3 x ULN; (b) > 5 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN

- Total bilirubin: > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. All treatment-emergent liver-related abnormalities will be summarized for the randomized phase CCI [redacted]. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Bone Safety Analysis

The BMD-related analyses for randomized phase summaries will be based on subjects in the Hip or Spine DXA Analysis Set, CCI [redacted] will be based on subjects in the CCI [redacted] Spine DXA Analysis Set. Summaries for the entire study treatment period will be based on subjects in the CCI [redacted] Spine DXA Analysis Set. The analyses of bone biomarkers, fracture events and bone events will be based on subjects in the Safety Analysis Set, CCI [redacted] will be based on subjects in the CCI [redacted] .CCI [redacted]

7.3.1. Bone Mineral Density (BMD)

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

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

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	$-2.5 \leq$ 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.

The number and percentage of subjects in each category based on percentage change from baseline in hip BMD and spine BMD (> 7% decrease, > 5% to ≤ 7% decrease, > 3% to ≤ 5% decrease, > 1% to ≤ 3% decrease, > 0 to ≤ 1% decrease, 0 to ≤ 1% increase, > 1% to ≤ 3%

increase, > 3% to ≤ 5% increase, > 5% to ≤ 7% increase, > 7% increase) will be summarized by treatment group and visit.

The above analyses will be repeated in the subgroups based on baseline renal function ($eGFR_{CKD-EPI}$ < 50 ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2).

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 for the entire study treatment period for subjects in the DXA Analysis Set. Listings of hip and spine DXA results will be provided.

7.3.2. Bone Biomarkers

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

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

Median (Q1, Q3) percentage change from baseline in bone biomarkers over time will be plotted by treatment group for the entire study treatment period for subjects in the Safety Analysis Set. A listing of bone biomarker data will be provided.

7.3.3. Fracture Events

The PTs for fracture events were defined based on HLGT of Fractures from current version of MedDRA. Treatment-emergent fracture events will be summarized based on the identified PTs from the HLGT. The number and percentage of subjects who experienced fracture events will be summarized by treatment group for the randomized phase CCI [redacted]. 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 for the randomized phase.

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 based on the Medical Search Term (MST) of Bone Disorders on current version of MedDRA. The number and percentage of subjects who experienced treatment-emergent bone events will be summarized by treatment group for the randomized phase CCI [redacted]. A data listing of bone events will be provided.

7.4. Renal Safety Analysis

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 increase from baseline in creatinine of at least 0.3 mg/dL or
- Baseline $eGFR_{CKD\text{-}EPI} \geq 50$ mL/min/1.73 m^2 and confirmed postbaseline $eGFR_{CKD\text{-}EPI} < 50$ mL/min/1.73 m^2 or
- Confirmed $eGFR_{CKD\text{-}EPI} < 30$ mL/min/1.73 m^2 or
- Confirmed phosphorous < 2 mg/dL

Treatment-emergent confirmed renal abnormalities will be summarized for randomized phase CCI [redacted]. All confirmed renal abnormalities including those occurred during the 24-week treatment-free follow-up period will be listed.

7.4.2. Serum Creatinine and Serum Cystatin C

The baseline and change from baseline in serum creatinine and serum cystatin C will be summarized using descriptive statistics for the entire study period.

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

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

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

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

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

Table 7-2. Method of Serum Creatinine Correction

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

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

7.4.3. Estimated Glomerular Filtration Rate

The following formulae will be used to calculate eGFR:

- CG:

  $eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

  where weight is actual total body mass in kilograms, and SCr is serum creatinine.

- CKD-EPI Creatinine Based:

  $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2) = 141 × min(SCr/κ,1)$^{\alpha}$ × max(SCr/κ,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 $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ creatinine}$ and $eGFR_{CKD\text{-}EPI,\ cysC}$ at each postbaseline visit will be provided during the entire study treatment period.

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

The number and proportion of subjects in each stage of chronic kidney disease (CKD) will be summarized by baseline stages of CKD at each postbaseline visit for the entire study treatment period based on subjects in the Safety Analysis.

The stages of CKD by estimated GFR by CG, CKD-EPI creatinine, CKD-EPI Cystatin C are defined in Section 5.2.

Median (Q1, Q3) change from baseline in $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ creatinine}$ and $eGFR_{CKD\text{-}EPI,\ cysC}$ over time will be plotted for the entire study treatment period for subjects in the Safety Analysis Set.

7.4.4. Treatment-emergent Proteinuria (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) will be summarized by treatment group for the randomized phase [redacted]. A listing of subjects with treatment-emergent proteinuria will be provided.

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

Baseline, postbaseline, change from baseline and percentage change from baseline in urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by treatment group and visit using descriptive statistics during the entire study treatment period. Median (Q1,

Q3) percentage change from baseline over time will be plotted by treatment group for the entire study treatment period for subjects in the Safety Analysis Set.

7.4.6. Proteinuria by Quantitative Assessment

Baseline, postbaseline, changes from baseline, and percentage change from baseline in UPCR and UACR will be summarized by treatment group and visit using descriptive statistics, for the entire study treatment period. The number and proportion of subjects with UPCR ≤ 200 mg/g versus > 200 mg/g will be summarized by baseline category for each postbaseline visit during the entire study period {KDIGO Guideline Development Staff 2013} .

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

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

7.4.7. Other Renal Biomarkers

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

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

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

where TRP (tubular 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 during entire study period.

7.4.8. Cr EDTA

In addition, the baseline, postbaseline, and change from baseline of surface area corrected value (mL/min/1.73 m^2) from Cr EDTA renal scan will be summarized by treatment group and visit using descriptive statistics during the entire study treatment period.

The number and proportion of subjects in each stage of chronic kidney disease (CKD) will be summarized by baseline stages of CKD at each postbaseline visit for the entire study treatment period based on subjects in the Safety Analysis.

The stages of CKD by estimated GFR by Cr EDTA is defined in Section 5.2.

7.5. Body Weight

Body weight at each visit and change from baseline in body weight will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group for each postbaseline analysis window, during the randomized phase, CCI [redacted] and the entire study treatment period separately. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.6. Prior Hepatitis B Medications

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

7.7. 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.

Summaries of concomitant medications using the number and percentage of subjects for each treatment group will be provided by WHO preferred name for the randomized phase based on the Safety Analysis Set CCI [redacted]. Subject will be counted only once for each preferred name. The summary will be ordered by overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

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 randomized 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 randomized study drug
- The month and year of stop of the medication is before the date of the first dose of randomized study drug

CCI [redacted]

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

CCI [redacted]

7.8. Other Safety Measures

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

7.9. Changes From Protocol-Specified Safety Analyses

Treatment-emergent AE and lab abnormality in randomized phase was defined as any AE or lab abnormality that begins on or after the first dose date of study drug up to the last dose date in the protocol, and is updated in this SAP. Treatment-emergent AE occurring in the randomized phase is defined as any AE with onset date on or after the first dose date of the randomized study and no later than the minimum of the randomized study drug stop date + 3 days CCI [redacted], if applicable for the randomized phase. Treatment-emergent laboratory abnormalities occurring in the randomized phase are defined as values that increase by at least 1 toxicity grade from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days CCI [redacted] for the randomized phase. This change was made as labs performed 1-2 days after study drug stopped were being excluded causing the measurement for the timepoint to be missed, even though protocol specified visit windows allowed for labs to be performed in a short period after the study drug was stopped.

8. REFERENCES

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

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

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

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

9. SOFTWARE

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

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 MMM YYYY)	Section	Summary of Revision	Reason for Revision

11. APPENDICES

Appendix 1. Study Procedures Table

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	TFFU[q]
	Visit Windows[a]		± 3 Days										± 7 Days
Written Informed Consent	X												
Review of Inclusion/Exclusion Criteria	X	X											
Medical History, including HBV history	X	X											
Review Concomitant Medications	X	X	X		X		X	X	X	X	X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X
Complete Physical Examination including vital signs, and weight	X	X					X		X		X		
Height	X												
Symptom-directed Physical Exam			X		X			X		X			X
Body weight	X	X	X		X		X	X	X	X	X		X
Vital Signs[b]	X	X	X		X		X	X	X	X	X		X
Randomization		X											
DXA[c] (spine & hip)	X								X		X		
FRAX® Fracture Risk Assessment Tool		X											

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	TFFU[q]
	Visit Windows[a]		± 3 Days										± 7 Days
Cr EDTA renal scan		X									X		
Study Drug Accountability			X		X		X	X	X	X	X		
Study Drug Dispensed/Retrieved		X	X		X		X	X	X	X	X		
Dosing in-clinic[d]			X		X								
Serum Chemistry and Liver Function Tests[e]	X	X	X		X		X	X	X	X	X		X
$eGFR_{CKD-EPI}$	X	X	X		X		X	X	X	X	X		X
Hematology	X	X	X		X		X	X	X	X	X		X
Cystatin C (for estimated GFR)	X	X	X				X		X		X		X
Plasma HBV DNA Levels	X	X	X		X		X	X	X	X	X		X
Serum HBsAg (qualitative)[f]	X	X							X		X		X
Serum HBeAg (qualitative)[f]	X	X							X		X		X
Sample collection for HBV Resistance Surveillance[g]		X	X		X		X	X	X	X	X		X
HIV-1, HDV, HCV	X												
α-fetoprotein	X								X		X		
Fibrotest®		X							X		X		

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	TFFU[q]
	Visit Windows[a]		± 3 Days										± 7 Days
Vitamin D		X							X		X		
Whole blood for PBMC		X							X		X		
Plasma PK[m]		X	X		X		X	X	X	X	X		
Fasting Blood for Bone Biomarkers[h]		X	X				X		X		X		
Fasting Blood for Renal Biomarkers[h]		X	X				X		X		X		
Fasting Urine for Renal Biomarkers[i]		X	X				X		X		X		
Fasting Metabolic Panel[o]		X							X		X		
Serum Pregnancy Test[j]	X												
Urine Pregnancy Test[j]		X	X		X		X	X	X	X	X		X
Urinalysis	X	X	X				X		X		X		X
Urine drug screen	X												
CCI													
CCI													
Health Related Quality of Life Surveys[l]		X							X		X		

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	TFFU[q]
	Visit Windows[a]		± 3 Days									CCI	± 7 Days
Imaging Test[n]	X												
CCI													

a The out of visit window is ± 3 days until Week 48, CCI , and ± 7 days for TFFU visits.
b Vital signs include blood pressure, pulse, respiration rate, and temperature.
c The initial DXA will be performed during Screening and should be completed at least 14 days prior to the first dose of study drug. The Week 48 DXA window is – 3 days only. DXA is required for Early Discontinuation (ED) visit if not done within the last 24 weeks.
d It is preferred that subjects take their study drug according to a morning dosing schedule; subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing and provide the single PK sample being collected at Week 4 and 8 visits.
e Serum chemistry and Liver Function Tests: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At Baseline, Weeks 24, 48, CCI ED, subject will be fasting for serum glucose and metabolic panel. Coagulation panel will be done at Screening and then as a reflex only test for ALT flares.
f Qualitative HBsAg and HBeAg will be performed at Screening, Baseline (BL), Weeks 24, 48, CCI and ED. HBeAb and HBsAb testing will be performed as reflex testing as needed.
g Sequence analysis of the HBV pol/RT for possible resistance mutation(s) may be attempted for any subject that experiences viremia (HBV DNA > 69 IU/mL).
h Blood for selected bone biomarkers and renal biomarkers will be collected in a fasted state. Required for ED visit if the last sample was collected > 24 weeks prior.
i Urine for selected renal biomarkers will be collected in a fasted state. Required for ED visit if the last sample was collected > 24 weeks prior.
j For female subjects of childbearing potential, the serum beta-HCG test will be performed at Screening. Urine test will be performed at all other visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy tests should include prevention counseling.
[redacted]
l Health Related Quality of Life surveys included in this study are: SF-36, CLDQ, and WPAI. The surveys will be administered at BL, Weeks 24, 48, CCI and Early Discontinuation Visits, if applicable.
m At Weeks 8 and 24 the plasma PK samples should be collected between 15 minutes and 4 hours post-dose.
n At Screening, α-fetoprotein (AFP) will be measured and subjects with an AFP >50 ng/mL or other findings concerning HCC must undergo imaging test (eg, CT scan) to rule out HCC.
o Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides)
[redacted]
q Subjects who have received at least one dose of TAF and discontinue treatment prematurely CCI will be followed every 4 weeks for 24 weeks off treatment in accordance with TFFU visits or until initiation of alternative CHB therapy, whichever comes first.

Appendix 2. Data Collection of COVID-19 Data

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

Data Collection

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

Determination of Missed and Virtual Visits

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

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

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

iii. Otherwise result is missing

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

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

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	12-Jun-2021 05:11:08
PPD	Clinical Research eSigned	14-Jun-2021 15:55:41