# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Title:** | A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection |
| **Name of Test Drug:** | Tenofovir disoproxil fumarate (Viread®) |
| **Study Number:** | GS-US-174-0144 |
| **Protocol Version:** | Amendment 4 |
| **Protocol Date:** | 04 August 2016 |
| **Analysis Type:** | Week 192 Analysis |
| **Analysis Plan Version:** | Version 1 |
| **Analysis Plan Date:** | 15 October 2020 |
| **Analysis Plan Authors:** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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| | |
|---|---|
| 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) |
| ATC | anatomical therapeutic chemical |
| AUC | area under the curve |
| BLQ | below the limit of quantitation |
| BMD | bone mineral density |
| BMI | body mass index |
| bsAP | bone specific alkaline phosphatase |
| CDC | Centers for Disease Control and Prevention |
| 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 |
| CRF | case report form |
| CSR | clinical study report |
| 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 |
| FEPO4 | fractional excretion of filtered phosphate |
| FEUA | fractional excretion of uric acid |

| | |
|---|---|
| GCP | Good Clinical Practice (Guidelines) |
| GFR | glomerular filtration rate |
| Gilead | Gilead Sciences, Inc. |
| HAV | hepatitis A virus |
| 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 |
| IWRS | interactive web response system |
| LDL | low density lipoprotein |
| LFT | liver function test |
| LLN | lower limit of the normal range |
| LOQ | limit of quantification |
| LLT | lower-level term |
| LMS | lambda-mu-sigma |
| LOD | limit of detection |
| M = E | Missing = Excluded |
| M = F | Missing = Failure |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | milliliter(s) |
| MH | Mantel-Haenszel |
| OC | Osteocalcin |
| P1NP | procollagen type 1 N-terminal propeptide |
| PA | Protocol Amendment |
| PBMC | peripheral blood mononuclear cell |
| PK | pharmacokinetic |
| PO | orally |
| pol/RT | polymerase/reverse transcriptase |
| PP | per protocol |
| PT | preferred term |
| PTH | parathyroid hormone |
| Q | Quartile |

| | |
|---|---|
| Q1 | first quartile |
| Q3 | third quartile |
| qHBsAg | quantitative hepatitis B surface antigen |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SE | standard error |
| SOC | system organ class |
| TDF | tenofir DF, tenofovir disoproxil fumarate (Viread®) |
| TFFU | treatment free follow-up |
| TFLs | tables, figures, and listings |
| TFV | Tenofovir |
| TmP | tubular maximum reabsorption rate of phosphate |
| TRP | tubular reabsorption of phosphate |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in the tables, figures, and listings (TFLs) of the clinical study report (CSR) for the Final Week 192 analysis of Study GS-US-174-0144. All primary and secondary endpoints had been implemented in the Week 48 analysis, and details can be found in the Week 48 SAP. This SAP will focus on the corresponding analysis at Week 192, as applicable. Data collected up to Week 192 will be summarized. An overall of adverse events, serious adverse events, and laboratory abnormality during TFFU will also be presented. CCI [redacted] This SAP is based on the study protocol Amendment 4 dated 04 August 2016 and the electronic case report forms (eCRF). The double-blind treatment duration and primary endpoint were modified from Week 72 to Week 48 per the US Food and Drug Administration's recommendation in study protocol Amendment 3 dated 29 February 2016. The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

## 1.1. Study Objectives

The primary objective of this study is:

- To evaluate the antiviral efficacy at Week 48 of tenofovir disoproxil fumarate (TDF; Viread®) versus placebo in pediatric subjects (aged 2 to < 12 years) with chronic hepatitis B infection

The key secondary objective is:

- To evaluate the proportion of subjects with hepatitis B e antigen (HBeAg) seroconversion at Week 48 (in subjects with baseline HBeAg sero-positivity)

Other secondary objectives are:

- To characterize the safety and tolerability profile of TDF at Week 48 in pediatric subjects (aged 2 to < 12 years) with chronic hepatitis B infection
- To evaluate the biochemical and serological responses at Week 48 to TDF versus placebo
- To evaluate the incidence of potential resistance mutations to TDF at Week 48 in the hepatitis B virus (HBV) polymerase/reverse transcriptase (pol/RT)
- To assess the pharmacokinetics (PK) of tenofovir in subjects receiving the tablet formulation

## 1.2. Study Design

### Design Configuration and Subject Population

GS-US-174-0144 is a Phase 3, randomized, prospective, double-blind study comparing the antiviral efficacy, safety, and tolerability of TDF to placebo at Week 48 in pediatric subjects with chronic HBV infection.

### Treatment Groups and Randomization

One hundred TDF-naïve pediatric subjects aged 2 to <12 years, with chronic HBV infection (CHB; either HBeAg-positive or HBeAg-negative), HBV DNA ≥ $10^5$ copies/mL and alanine aminotransferase (ALT) ≥ 1.5 × upper limit of normal (ULN) at screening, are planned to be randomized in a 2:1 ratio to the following 2 treatment groups:

- Treatment A (N  67): TDF orally (PO) once daily for 48 weeks
- Treatment B (N  33): matching placebo PO once daily for 48 weeks

Subjects will be randomly assigned to treatment groups using centralized randomization via the interactive web response system (IWRS), with randomization stratified by age at enrollment (2 to <6 and 6 to <12 years) and geographical location of study site (North America/Europe and Asia). Subjects will be enrolled from approximately 35 centers from the following regions:
(1) North America including the United States, (2) Europe including Romania, and (3) Asia including India, South Korea, and Taiwan.

### Key Eligibility Criteria

At screening, pediatric subjects (2 to < 12 years of age) with chronic HBeAg-positive or HBeAg-negative HBV infection (hepatitis B surface antigen [HBsAg]-positive for at least 6 months; with HBV DNA ≥ $10^5$ copies/mL, ALT ≥ 1.5 × ULN and creatinine clearance ≥ 80 mL/min/1.73 $m^2$ at screening by the Schwartz formula) will be eligible for the study. Subjects must be naive to TDF but could have received interferon-alfa and/or other oral anti-HBV nucleoside/nucleotide therapies. Subjects experienced on oral anti-HBV nucleoside/nucleotide therapy must have discontinued therapy ≥ 16 weeks prior to screening (in order to avoid on-treatment ALT flare if randomized to receive placebo treatment). Subjects must have discontinued interferon-alfa ≥ 6 months prior to screening. Subjects must be without evidence of co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV) or acute hepatitis A virus (HAV). Subjects with a history of significant renal disease, bone disease, decompensated liver disease, evidence of hepatocellular carcinoma (ie, α fetoprotein > 50 ng/mL), or any chronic liver disease not related to HBV infection will not be eligible for the study.

**Study Periods/Phases**

The duration of randomized, double-blind treatment is 48 weeks.

As per Protocol Amendment 4, after 48 weeks of blinded randomized treatment, each subject will switch to open-label TDF treatment for an additional 144 weeks (ie through Week 192). Subjects under Protocol Amendment 3, wherein the primary analysis was planned for Week 72, who were treated beyond Week 48 of blinded randomized treatment, were to switch to open-label TDF at the Week 72 visit and then continue on open-label treatment until Week 192. Total study drug treatment period is 192 weeks for all enrolled subjects.

CCI [redacted]

Subjects who permanently discontinue study drug or complete the study at Week 192 CCI [redacted] will be followed for 24 weeks off treatment or up to initiation of active treatment, whichever occurs first. CCI [redacted]

**Schedule of Assessments**

Plasma HBV DNA levels, laboratory analyses (serum chemistry, liver tests, hematology, and urinalysis), pregnancy test (females of childbearing potential only), vital signs, adverse events and concomitant medications will be measured or assessed at Screening, Baseline, Weeks 4, 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, then every 12 weeks thereafter until the end of the study (and at Early Discontinuation CCI [redacted]). HBV serology (HBsAg, HBeAg, and reflex hepatitis B e antibody [HBeAb] and hepatitis B surface antibody [HBsAb]) will be conducted at Screening, Baseline, Weeks 16, 32, 48, 64, 72, 80, and 96, then every 12 weeks through the end of study (and at Early Discontinuation CCI [redacted]).

Dual energy x-ray absorptiometry (DXA) scans of the spine and whole body will be performed at Baseline, and Weeks 24, 48, 72, and 96, then annually until completion of the study (and at Early Discontinuation CCI [redacted]). Bone biochemical markers will be measured at Screening, Baseline, every 24 weeks through Week 96, then annually until the end of study (and at Early Discontinuation CCI [redacted]). DXA and bone biochemical markers will also be required at the time of switching from placebo to TDF if the last measurement was performed > 12 weeks prior to switch.

Complete physical examinations (including Tanner Staging starting at Baseline) will be performed at Screening, Baseline, Week 24 and then every 24 weeks through the end of study (and at Early Discontinuation, if applicable) CCI [redacted]

Determination of HBV viral genotype (A-H) will be performed at baseline for all subjects.

Subjects will maintain a Subject Dosing Diary Card to monitor subjects' compliance to study treatment at Weeks 4, 24, and 56. Subjects will maintain a diary for 10 days prior to the next visit. CCI [redacted]

Resistance surveillance will be conducted at Baseline for all subjects and attempted for all viremic subjects (HBV DNA ≥ 69 IU/mL [400 copies/mL]) at Weeks 48, 96, 144, and 192 (and at Early Discontinuation, if applicable).

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[redacted]

[redacted]

## 1.3. Sample Size and Power

A sample size of 100 subjects (67 TDF, 33 placebo) would provide at least 85% power to detect a 20% treatment difference between TDF and placebo in the primary efficacy endpoint, assuming that the response rate in the TDF arm is 21% and the response rate in the Placebo arm is 1%. This calculation is based on a two-sided Fisher's exact test with a significance level of 0.05. A similar placebo-response rate was observed in study GS-US-174-0115.

The US Food and Drug Administration (FDA) allowed the study to stop enrollment early, with a total of 90 subjects randomized (with 89 subjects treated), due to difficulty in enrolling subjects and to limit exposure of subjects to placebo. The reduced sample size is unlikely to impact the power of the study, even adjusting for the modification of the primary endpoint from Week 72 to Week 48, as the originally assumed response rate in the TDF arm was only 21%. If the assumed response rate for the TDF arm is adjusted to be 80%, which is similar to the observed TDF-response rate from the adolescent CHB GS-US-174-0115 study (86.5% at Week 48), then this study will have above 85% power with a sample size of approximately 90 subjects.

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Data Monitoring Committee Analysis

An independent external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The DMC will review the progress and safety of this study approximately every 24 weeks after the first subject is randomized. During the duration of the open-label phase of the study, the DMC will convene approximately every 52 weeks.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

## 2.2. Week 48 Analysis (Primary Analysis)

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

## 2.3. Week 192 Analysis

The statistical analysis for the study will be conducted after all subjects have completed Week 192 visit or prematurely discontinued study treatment prior to Week 192, 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 Week 192 analysis. No additional PK analysis is planned for the Week 192 report. The primary Week 48 analysis had been described in the Week 48 SAP and won't be repeated in the Week 192 analysis. Additional analyses may be performed if warranted.

# 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 Randomized Analysis Set 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 the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and region will be included in the listings, as space permits.

## 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. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and overall. A listing of subjects excluded from analysis sets will also be provided.

### 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 will include 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-blind phase. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire double-blind treatment duration. This is the primary analysis set for safety analyses.

### 3.1.3. Open-Label Safety Analysis Set

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

### 3.1.4. Treatment-Free Follow-up Safety Analysis Set

The treatment-free follow-up (TFFU) Safety Analysis Set includes all randomized subjects who entered the TFFU period. Subjects will be analyzed according to the treatment they actually received during the double-blind phase.

### 3.1.5. Full Analysis Set

The Full Analysis Set (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.

### 3.1.6. Serologically Evaluable Full Analysis Set

### 3.2. 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 HBeAg positive and HBeAb negative or missing at baseline. Subjects will be analyzed according to the treatment to which they were randomized.

3.2.1.1. 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 HBsAg positive, defined as HBsAg level ≥ 0.07 IU/mL, and HBsAb negative or missing at baseline. Subjects will be analyzed according to the treatment to which they were randomized.

### 3.2.2. DXA Analysis Set

3.2.2.1. 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 bone mineral density (BMD) values. Subjects will be analyzed according to the treatment they actually received during the double-blind phase.

3.2.2.2. Whole Body DXA Analysis Set

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

### 3.2.3. Open-Label DXA Analysis Set

3.2.3.1. Open-Label Spine DXA Analysis Set

The Open-Label Spine DXA Analysis Set will include all subjects who were randomized and had received at least 1 dose of study drug and had nonmissing open-label baseline spine bone mineral density (BMD) values. Subjects will be analyzed according to the treatment they actually received during the double-blind phase.

3.2.3.2. Open-Label Whole Body DXA Analysis Set

The Open-Label Whole Body DXA Analysis Set will include all subjects who were randomized and had received at least 1 dose of study drug and had nonmissing open-label baseline whole body BMD values. Subjects will be analyzed according to the treatment they actually received during the double-blind phase.

## 3.3. Subject Grouping

Subjects will be grouped into the following treatment groups:

- Double-blind phase: TDF and Placebo
- Open-label phase: TDF and Placebo-TDF (including Placebo-TDF at Week 48, Placebo-TDF at Week 72, and total)

## 3.4. Strata and Covariates

Randomization was stratified by age (2 to <6 and 6 to <12 years at the time of enrollment) and geographical location of study site (North America/Europe, and Asia). For all stratified analyses, age at baseline (<6 and ≥6 years) and geographical location of study site (North America/Europe, and Asia) will be used. If the number of subjects in a particular stratum is too small, this stratum may be combined with other strata for analysis. If there are discrepancies in stratification factor values between the IWRS and the clinical database at screening or baseline, the values recorded in the clinical database at baseline (or screening, if baseline is missing) will be used for stratified analyses.

## 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 a Missing Failure (M F) approach. Sensitivity analyses will also be performed using a Missing Excluded (M E) approach.

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

### 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 data analysis.

## 3.6. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the eCRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

Non-PK 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:

A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

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

The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

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

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate. Specifically, logarithm (base 10) will be used to transform HBV DNA and quantitative HBsAg data.

## 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 blinded study drug was taken, as recorded on the Study Drug Administration eCRF.

**Study days** are calculated relative to Study Day 1. For events that occurred on or after 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 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.

**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, study days are calculated as (visit date Open-Label Study Day 1 + 1).

**Follow-up days** are for visits occurred during 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 the 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 during open-label treatment and 24-week treatment free follow up, are 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 the 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 the 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 during 24-week treatment-free follow-up, 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 clinical visit dates, 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 for the double-blind phase** is defined as the last nonmissing value obtained on or prior to Study Day 1.

**Baseline value for the open-label phase** is defined as the last nonmissing value obtained on or prior to Open-label Study Day 1.

**Baseline value for the TFFU phase** is defined as the last nonmissing value obtained on or prior to the Last Dose Date + 3 days.

### 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 3-1 to Table 3-3) apply to baseline and on-treatment assessments only; ie, data collected during the double-blind phase and open-label phase. For summaries and analyses, assessments will first be categorized into on-treatment assessments occurring during the double-blind or open-label phase, before applying analysis windows.

For subjects who completed blinded study drug and entered the open-label phase, laboratory and DXA assessments that occurred during the period from the first dose date of blinded study drug up to and including the minimum of the Last Dose Date of Blinded Study Drug + 3 days and the Open-label Study Day 1, will be considered as on-treatment during the double-blind phase. If a subject prematurely discontinued blinded study drug or did not enter open-label phase after completion of blinded study drug, then on-treatment assessments during the double-blind phase will be defined as assessments that occurred during the period from the first dose date of blinded study drug to the Last Dose Date + 3 days.

For subjects who entered the open-label phase, on-treatment assessments during the open-label phase will be defined as assessments that occurred during the period from Open-label Study Day 1 up to the Last Dose Date + 3 days.

Follow-up assessments during the treatment free follow-up (TFFU) phase will be defined as assessments that occurred during the period after the Last Dose Date + 3 days up to the Last Study Date. Assessments during this period are considered follow-up.

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The analysis windows for HBV DNA, hematology, serum chemistry and liver tests, urinalysis, urine pregnancy test, height, weight, and vital sign assessments are presented in Table 3-1.

**Table 3-1. Analysis Windows for HBV DNA, Hematology, Serum Chemistry and Liver Tests, Urinalysis, Urine Pregnancy Test, Height, Weight, and Vital Sign Assessments**

| Visit ID | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | | | 1 |
| Week 4 | 28 | 2 | 41 |
| Week 8 | 56 | 42 | 83 |
| Week 16 | 112 | 84 | 139 |
| Week 24 | 168 | 140 | 195 |
| Week 32 | 224 | 196 | 251 |
| Week 40 | 280 | 252 | 307 |
| Week 48 | 336 | 308 | 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 | 1049 |
| Week 156 | 1092 | 1050 | 1133 |
| Week 168 | 1176 | 1134 | 1217 |
| Week 180 | 1260 | 1218 | 1301 |
| Week 192 | 1344 | 1302 | 1385 |

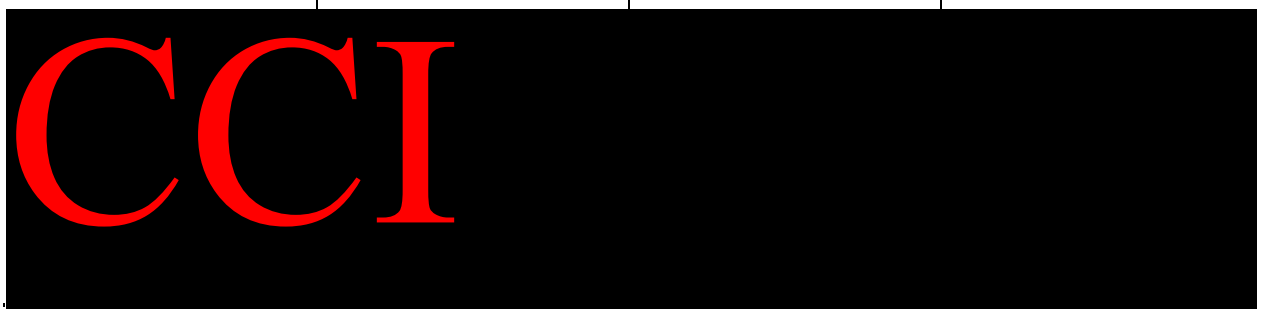
CCI [redacted]


The analysis windows for spine and whole body bone mineral density (BMD) results from DXA and bone biochemical markers: urine bicarbonate, urine n-telepeptide, serum c-telopeptides, osteocalcin, bone-specific alkaline phosphatase, serum parathyroid hormone (PTH), vitamin D levels (25-hydroxy) and (1,25-dihydroxyvitamin), fasting serum creatinine and fasting phosphate, urine creatinine (spot) and phosphate, and renal phosphate threshold (tubular maximum reabsorption rate of phosphate [TmP]/glomerular filtration rate [GFR]), are presented in Table 3-2.

**Table 3-2. Analysis Windows for Spine and Whole Body From DXA and Bone Biochemical Markers**

| Visit ID | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | | | 1 |
| Week 24 | 168 | 2 | 251 |

| Visit ID | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Week 48 | 336 | 252 | 419 |
| Week 72 | 504 | 420 | 587 |
| Week 96 | 672 | 588 | 839 |
| Week 144 | 1008 | 840 | 1175 |
| Week 192 | 1344 | 1176 | 1511 |




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

**Table 3-3. Analysis Windows for HBV Serology and qHBsAg**

| Visit ID | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | | | 1 |
| Week 16 | 112 | 2 | 167 |
| Week 32 | 224 | 168 | 279 |
| Week 48 | 336 | 280 | 391 |
| Week 64 | 448 | 392 | 475 |
| Week 72 | 504 | 476 | 531 |
| Week 80 | 560 | 532 | 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 | 1049 |
| Week 156 | 1092 | 1050 | 1133 |
| Week 168 | 1176 | 1134 | 1217 |
| Week 180 | 1260 | 1218 | 1301 |
| Week 192 | 1344 | 1302 | 1385 |


Data collected after the TFFU phase will be considered as follow-up visits. The analysis windows for follow-up assessments are presented in Table 3-4 and Table 3-5.

**Table 3-4. Analysis Windows for Follow-up Assessments Except HBV Serology**

| Visit ID | Nominal Follow-Up Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Follow-Up Baseline | | | 4 |
| Follow-Up Week 4 | 28 | 5 | 41 |
| Follow-Up Week 8 | 56 | 42 | 69 |
| Follow-Up Week 12 | 84 | 70 | 97 |

| Visit ID | Nominal Follow-Up Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Follow-Up Week 16 | 112 | 98 | 125 |
| Follow-Up Week 20 | 140 | 126 | 153 |
| Follow-Up Week 24 | 168 | 154 | 181 |

**Table 3-5. Analysis Windows for Follow-up HBV Serology and qHBsAg**

| Visit ID | Nominal Follow-Up Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Follow-Up Baseline | | | 4 |
| Follow-Up Week 24 | 168 | 5 | 333 |

### 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 of the double-blind and open-label phases, the last available record on or prior to the first dose of blinded and open-label study drug will be selected, respectively. If there are multiple records with the same time or no time recorded on the same day for numeric observations, the average will be computed for that day, except for HBV DNA [IU/mL] and quantitative HBsAg [IU/mL], where the geometric mean will be computed instead. 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 positive will be selected over negative for HBeAb and HBsAb.

The following specified rules will be used for postbaseline visits:

- **ALT:** The largest value will be included in the analysis when 2 or more ALT values occur within the same visit window.
- **BMD:** The latest record in the window will be selected.
- **HBV DNA and quantitative HBsAg:** The record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the geometric mean will be taken.
- **Serology:** For HBeAg, HBeAb, 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 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 exist in a window, then records will be chosen as follows:

  The most conservative value 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 enrolled in each region, country, and by each investigator will be summarized by treatment group and overall using the Randomized Analysis Set. The number and percentage of subjects enrolled in each randomization stratum will be summarized based on IWRS data. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

## 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, subjects not randomized, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized with reasons for subjects not randomized, subjects in the Randomized Analysis Set, subjects randomized and not treated, and subjects in the Safety Analysis Set.

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

**Double-Blind Phase**

- Completed double-blind study drug

  Completed double-blind study drug at Week 72

  Completed double-blind study drug at Week 48

- Premature discontinuation of double-blind study drug (with summary of reasons for discontinuation of double-blind study drug)

**Open-Label Phase**

- Entered open-label phase at Week 72
- Entered open-label phase at Week 48
- Completed open-label study drug
- Premature discontinuation of open-label study drug (with summary of reasons for discontinuation of open-label study drug)

CCI [redacted]

**Started another HBV therapy**

**TFFU Phase**

- Entered TFFU
- Continuing TTU
- Completed TFFU
- Discontinued TFFU (with summary of reasons for discontinuation of the study)

**Study Completion**

- Continuing study
- Completed protocol-planned duration of study
- Premature discontinuation of study (with summary of reasons for premature discontinuation of study)

No inferential statistics will be generated. A flowchart will be provided to depict the disposition. Also, the following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Subject disposition including reasons for premature study drug or study discontinuation
- Screen failed subjects with reasons for screen failure

### 4.3. Extent of Open-Label Study Drug Exposure and Adherence

Exposure data described below will be summarized open-label phase.

### 4.3.1. Duration of Exposure to Open-Label Study Drug

Duration of exposure to open-label study drug will be defined as (last dose date of open-label study drug first dose date of open-label 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).

Duration of exposure to open-label 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.

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

### 4.3.2. Adherence with Open-Label Study Drug Regimen

Study drug regimen adherence will be computed based on data from study drug accountability forms for open-label phase.

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

$$\text{Adherence (\%)} = 100 \times \frac{\text{Amount of Open-Label Study Drug Taken}}{\text{Amount of Open-Label Study Drug Expected To Be Prescribed}}$$

If calculated adherence is greater than 100%, then adherence will be set to 100%.

A dispensation period will be defined as a single entry into the Study Drug Administration eCRF. If any open-labeled study drug bottle is not returned or unknown (missing return date or on-going) or the amount of open-labled study drug dispensed is missing, then all of the records for the corresponding dispensation period will be excluded from both denominator and numerator in the calculation. For a dispensation period where the amount of open-labeled study drug returned is missing (but a date of return is available), it is assumed the amount of open-labeled study drug returned is zero.

[1] Amount of open-labeled study drug taken is determined by first converting the amount of open-labeled study drug from the powder or tablet formulation into mg of TDF or matching placebo, then subtracting the total amount of open-labeled study drug returned from the total amount of open-labeled study drug dispensed.

Specifically, if open-labeled study drug is administered as the powder formulation, then the amount of open-labeled study drug is multiplied by 40 (ie, 40 mg of open-labeled study drug per 1 gram of powder). If open-labeled study drug was administered as the tablet formulation, then the amount of open-labeled study drug is multiplied by 150 mg, 200 mg, 250 mg or 300 mg as indicated by the dose unit of open-labeled study drug dispensed. After conversion, the total amount of open-labeled study drug taken is calculated as the total amount of open-labeled study drug dispensed (mg) across all dispensation periods minus the total amount of open-labeled study drug returned (mg) across all dispensation periods.

[2] Amount of open-labeled study drug prescribed can be calculated using the following three steps: (1) collapse, (2) impute, and then (3) sum.

1) The first step is to collapse the dispensation periods by first sorting them by dispensation date in increasing order, and then for all dispensation periods with the same dispensation date, collapse into one dispensation period by setting the return date for the collapsed dispensation period to be the maximum of the corresponding return dates. If multiple open-labeled study drug formulations (ie, powder or tablet and dosage) are dispensed on the same dispensation date, then the open-labeled study drug formulation selected to represent the collapsed dispensation period will be the open-labeled study drug formulation with the largest difference between the amount of open-labeled study drug prescribed and open-labeled study drug returned (in terms of mg of open-labeled study drug).

2) The next step is to impute the return dispensation date for the collapsed dispensation periods to be the **day prior** to the minimum of the return date + 1 day, date of first dose of open-label study drug, date of last dose of open-labeled study drug formulation + 1 day, and dose dispensation date for the next collapsed dispensation period. The date of first dose of open-label study drug and date of last dose of open-labeled study drug formulation can be found on the Study Drug Administration eCRF. If the subject did not take open-label study drug, then date of first dose of open-label study drug will be excluded from the calculation.

3) The last step is to sum across the amount of open-labeled study drug expected to be prescribed for each collapsed and imputed dispensation period. The amount of open-labeled study drug expected to be prescribed for a given dispensation period can be calculated by first converting the prescribed study drug formulation to mg of TDF or placebo, and then multiplying by the duration of treatment, defined as the imputed return date the dispensation date + 1 day.

   Specifically, for subjects who took open-labeled study drug as an oral powder on the date of dispensation, based on the weight on the date of dispensation (use last available weight if weight on that day is not available from the vital signs dataset), multiply the duration of treatment during by one of the following expected daily doses of open-labeled study drug:

   80 mg for 10 to <12 kg (22 to <26 lbs)
   100 mg for 12 to <14 kg (26 to <31 lbs)
   120 mg for 14 to <17 kg (31 to <37 lbs)
   140 mg for 17 to <19 kg (37 to <42 lbs)
   160 mg for 19 to <22 kg (42 to <49 lbs)
   180 mg for 22 to <24 kg (49 to <53 lbs)
   200 mg for 24 to <27 kg (53 to <60 lbs)
   220 mg for 27 to <29 kg (60 to <64 lbs)
   240 mg for 29 to <32 kg (64 to <71 lbs)
   260 mg for 32 to <34 kg (71 to <75 lbs)
   280 mg for 34 to <35 kg (75 to <77 lbs)
   or 300 mg for ≥35 kg (≥77 lbs).

For subjects who took open-labeled study drug as tablets on the date of dispensation, multiply the duration of treatment by 150 mg, 200 mg, 250 mg, or 300 mg for subjects weighing <22 kg (37 to <49 lbs), 22 to <28 kg (49 to <62 lbs), 28 to <35 kg (62 to <77 lbs), and ≥ 35 kg (≥77 lbs), respectively.

After calculating the amount of open-labeled study drug expected to be prescribed for each collapsed and imputed dispensation period, then the amount of open-labeled study drug expected to be prescribed in [2] is calculated by summing across all collapsed and imputed dispensation periods.

Adherence will be calculated for each subject for the entire open-label phase and up to Week 192. A descriptive and categorical [< 80%, 80 < 90%, 90 < 95%, and ≥ 95%] summary will be provided for subjects in the Safety Analysis Set by treatment group. No inferential statistics will be provided.

### 4.4. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study will be provided in a by-subject listing for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected. 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.

### 4.5. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic which has caused a disruption in the regular visit schedules for this study. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides how to handle special situations due to COVID-19 in the analysis.

#### 4.5.1. Protocol Deviations Due to COVID-19

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

### 4.5.2. 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 was collected as free text in the CRF comment fields. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 1.

# 5. BASELINE CHARACTERISTICS

Summaries of demographics and baseline characteristics using original data from the double-blind phase will be presented for subjects who are in the open-label phase. This will exclude subjects who prematurely discontinued prior to open-label baseline.

## 5.1. Demographics and Baseline Characteristics

Subject demographic data (ie, age (years), age group (<6 and ≥ 6 years), sex, race, ethnicity, and geographic region (North America/Europe, and Asia)) and baseline characteristics (ie, weight (kg), height (cm), body mass index [BMI] (kg/m$^2$), 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])), and corresponding weight, height, and BMI Z-scores (calculated using the lambda-mu-sigma (LMS) method based on the Centers for Disease Control and Prevention (CDC) growth chart {Centers for Disease Control and Prevention (CDC) 2016}), 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 using the Safety Analysis Set. Age will be calculated in years at the date of first dose of study drug.

Baseline disease characteristics will include a summary of HBV DNA level ($log_{10}$ IU/mL), HBsAg ($log_{10}$ IU/mL), HBsAg status (positive [HBsAg ≥ 0.07 IU/mL], negative [HBsAg < 0.07 IU/mL]), HBeAg and HBeAb status (positive, negative), ALT and asparatate aminotransferase (AST) values (U/L), corrected BMD (via DXA scan) and corrected Z-Scores for both spine and whole body, serum bone biochemical markers including: urine bicarbonate, urine n-telopeptide, serum c-telopeptides, osteocalcin, bone specific alkaline phosphatase, PTH, vitamin D levels (25-hydroxy) and 1, 25 (dihydroxy vitamin) D levels, fasting serum creatinine and phosphate, spot urine creatinine and phosphate, and renal phosphate threshold (TmP/GFR), and estimated GFR by the Schwartz formula using the Safety Analysis Set.

In addition, the following baseline disease characteristics will be summarized:

- ALT level based on central laboratory normal range (≤ 1.5 × ULN, > 1.5 × ULN - 5 × ULN, > 5 × ULN - 10 × ULN, > 10 ULN)
- ALT level based on AASLD normal range (ULN is 30 U/L for pediatric subjects; ≤ 1.5 × ULN, > 1.5 × ULN - 5 × ULN, > 5 × ULN - 10 × ULN, > 10 ULN)
- Previous Hepatitis B medication exposure (yes, no)
- Years positive for HBV
- HBV genotype (A, B, C, D, etc.); if genotype results at baseline are missing, genotype results post-baseline, if available, will be reported in this summary

By-subject listings will be provided to support the summaries of demographics and baseline characteristics and baseline disease characteristics tables.

## 5.2. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

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

# 6. EFFICACY ANALYSES

For Week 192 analyses, efficacy data will be summarized for both the double-blind phase and the open-label phase by treatment group. Subjects will be grouped as follows: TDF and Placebo-TDF, including Placebo-TDF at Week 48, Placebo-TDF at Week 72, and total. Two approaches will be used: (1) a Missing Failure (M F) approach and (2) a Missing Excluded (M E) approach. Unless otherwise specified, data will be summarized up to Week 192 using the M F and M E approaches. All efficacy data up to the data finalization, including data collected during CCI and the treatment-free follow-up phase, will be provided in the listings.

From Week 72 onward, if there are multiple HBV DNA test results, new assay from HBV DNA CAPCTM2.0-EDTA-CL-PS will be reported for the analysis. In the case of HBV DNA CAPCTM2.0-EDTA-CL-PS test result unavailable, the old assay from HBV DNA PCR TaqMan EDTA-CL-QT or HBV DNA CAP/CTM2.0-EDTA-CL test result will be included.

## 6.1. Primary Efficacy Endpoint

### 6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HBV DNA < 69 IU/mL (400 copies/mL) at Week 48. The Missing Failure (M F) approach will be employed for handling missing data. The primary efficacy endpoint was analyzed at Week 48 analysis and will not be repeated in the final analysis. Details were provided in the Week 48 SAP.

## 6.2. Secondary Efficacy Endpoints

### 6.2.1. Definition of Secondary Efficacy Endpoints

For Week 192, secondary efficacy endpoints include:

- proportion of subjects with normal ALT and normalization of ALT
- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL] and normal ALT
- proportion of subjects with HBV DNA < 29 IU/mL [169 copies/mL]
- proportions of subjects with HBsAg loss and seroconversion in the Serologically Evaluable FAS for HBsAg Loss/Seroconversion
- sequence changes from baseline within the HBV polymerase for subjects who were viremic (HBV DNA ≥ 69 IU/mL [400 copies/mL]) at Weeks 48, 96, 144, 192 or Early Discontinuation; including subjects with confirmed virologic breakthrough

- cumulative incidence of at least a 4% decrease from baseline in bone mineral density of lumbar spine

- percent change from baseline in bone mineral density of lumbar spine

**Other endpoints of interest**

For Week 192, secondary efficacy endpoints to be evaluated in HBeAg-positive subjects include:

- proportion of subjects with HBeAg loss

- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL], normal ALT and HBeAg loss

- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL], normal ALT, and HBeAg seroconversion

For Week 192, secondary efficacy endpoints to be evaluated in subjects with abnormal ALT at baseline include:

- proportion of subjects with normalized ALT

- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL] and normalized ALT

For Week 192, secondary efficacy endpoints to be evaluated in HBeAg-positive subjects with abnormal ALT at baseline include:

- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL], normalized ALT and HBeAg loss

- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL], normalized ALT, and HBeAg seroconversion

For the Week 192 analysis, the following definitions will be used:

- HBsAg loss is defined as quantitative HBsAg < 0.07 IU/mL result at a postbaseline visit with baseline HBsAb negative or missing and HBsAg ≥ 0.07 IU/mL at baseline.

- HBsAg seroconversion is defined as HBsAg loss and a HBsAb test result change from HBsAb negative or missing at baseline to HBsAb positive at a postbaseline visit

- HBeAg loss is defined as a HBeAg test result change from HBeAg positive at baseline to HBeAg negative at a postbaseline visit with baseline HBeAb negative or missing

- HBeAg seroconversion is defined as HBeAg loss and a HBeAb test result change from HBeAb negative or missing at baseline to HBeAb positive at a postbaseline visit

- ALT normalization is defined as ALT greater than the upper limit of normal (ALT > ULN) as defined by the central laboratory normal range or AASLD normal range at baseline, but within normal range at a postbaseline visit

Borderline serology results will be imputed using the following rules:

- HBeAg borderline will be considered as 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 both the FAS and the Open-Label FAS, unless otherwise specified. Specifically, for endpoints including ALT normalization, subjects in both FAS and the Open-Label FAS with baseline abnormal ALT will be used. For HBsAg loss, HBsAg seroconversion, HBeAg loss, and HBeAg seroconversion, both the Serologically Evaluable FAS and the Open-Label Serologically Evaluable FAS for will be used.

Normal ALT and normalization of ALT analyses will each be repeated twice, once using the central laboratory ULN and once using the AASLD ULN. Normal ALT was defined as < 30 U/L for males and females based on the AASLD normal range for pediatric subjects between 0-12 years old.

Categorical secondary efficacy endpoints will be summarized by number and percentage of subjects that meet the endpoint. Analyses will also be repeated using the M F and the M E approach.

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

In addition, $\log_{10}$ HBV DNA (IU/mL) , ALT (U/L) and $\log_{10}$ HBsAg (IU/mL), and corresponding change from baseline values, will be summarized by visit using observed data.

The proportion of subjects with HBV DNA < 69 IU/mL [400 copies/mL] using both the M F and M E approach, proportion of subjects with HBeAg seroconversion using the M F approach only, proportion of subjects with normalized ALT by central lab and AASLD normal ranges, mean $\log_{10}$ HBV DNA (IU/mL), mean log10 HBsAg (IU/mL), and mean ALT (U/L) will be plotted with 95% CIs over time. Supportive listings for the analyses of the secondary endpoints will also be generated.

## 6.3. Changes From Protocol-Specified Efficacy Analyses

The FAS, DXA, Serologically Evaluable FAS for HBeAg Loss/Seroconversion, and Serologically Evaluable FAS for HBsAg Loss/Seroconversion, and Open-Label Analysis Sets were not defined in the protocol but was added in the SAP.

For HBV DNA analyses, the default will be to report measurements in IU/mL, which is the current clinically accepted way to describe this parameter, instead of copies/mL.

For ALT normalized and normal analyses, both the AASLD and central lab normal ranges will be used.

# 7. SAFETY ANALYSES

For the Week 192 analysis, adverse event and laboratory abnormality will be summarized for the open-label phase. Safety laboratory and vital sign data will be presented for both double-blind and open-label phase using the Safety Analysis Set. Bone biomarker and renal (CrCL, creatinine and phosphorus) data will be reported during both double-blind and open-label phase using the Safety Analysis Set as well the open-label phase using the Open-label Safety Analysis Set. An overall of adverse events, serious adverse events, and laborory abnormality during TFFU will be summarized. All safety data up to the data finalization, including data collected during CCI [redacted] will be included in data listings.

## 7.1. Adverse Events

### 7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (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

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

### 7.1.3. Relationship of Adverse Events to Study Drug

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

### 7.1.4. Serious Adverse Events

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

### 7.1.5. Treatment-Emergent AEs

7.1.5.1. Definition of Treatment Emergent

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

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

Post-treatment-emergent AEs occurring during the TFFU phase are defined as:

- Any AE with onset date after the last dose of study drug + 3 days

7.1.5.2. Incomplete Dates

If an AE onset date is incomplete or completely missing, the following rules will be used to determine if the AE is considered treatment emergent during the open-label phase:

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

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-labeled study drug permanently only: the month and year (or year) of onset date is the same as or before the month and year (or year) of the date of the last dose of the open-label study drug + 3 days, and
- End date is as follows:

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

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

  End date is completely missing

The event is post-treatment-emergent during the TFFU 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 day after the last dose date + 3 days

Events with Completely Missing Onset Date

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

The event is post-treatment-emergent during the TFFU phase if the following criteria are met:

- The (complete) end date is after the last dose date + 3 days, or
- The month and year (or year) of end date is the same or after the month and year (or year) of the day after the last dose date + 3 days, or
- End date is completely missing

### 7.1.6. 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 open-label phase 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 AE related to study drug, (5) any Grade 3 or 4 treatment-emergent AE related to study drug, (6) any Grade 2, 3, or 4 treatment-emergent AE related to study drug, (7) any treatment-emergent SAE, (8) any treatment-emergent SAE related to study drug, (9) any treatment-emergent AE leading to premature discontinuation of study drug, (10) any treatment-emergent AE leading to temporary study drug interruption, and (11) any TE death.

Treatment-emergent death occurring during the open-label phase refers to death that occurs between the first dose date of open-labeled study drug to the last dose date of open-labeled study drug + 3 days.

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 Open-Label Safety Analysis Set as follows:

- All treatment-emergent AEs summarized by SOC, HLT, and PT

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

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.

For post-treatment AEs during the TFFU phase, the overall summary and individual summaries will be provided only for the following:

- All post-treatment-emergent AEs
- Any Grade 3 and 4 post-treatment-emergent AEs
- All post-treatment-emergent SAEs

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

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Treatment-related SAEs
- Deaths

- AEs leading to premature discontinuation of study drug
- AEs leading to temporary interruption of study drug

## 7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the double-blind and open-label phase based on the Safety Analysis Set. Bone biomarker and renal laboratory (serum creatinine, phosphorus, CrCL) data will be reported for both double-blind and open-label phase using the Safety Analysis Set as well as open-label phase using the Open-label 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

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

### 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.

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 open-label phase are defined as values that increase by at least 1 toxicity grade from open-label baseline at any open-label postbaseline visit up to and including the last dose date of the open-label study drug + 3 days for those who discontinued open-label study drug permanently, or values that increase by at least 1 toxicity grade from open-label baseline at any open-label post-baseline visit for those who are still on open-label study drug. For the analyses of abnormalities occurring during open-label

treatment, open-label baseline will be considered to be the last available record on or prior to Open-Label Study Drug 1.

Post-treatment-emergent laboratory abnormalities occurring in the TFFU phase are defined as values that increase by at least 1 toxicity grade from TFFU baseline. For the analyses of abnormalities occurring during the TFFU phase, TFFU baseline will be the last available record on or prior to last dose date + 3 days.

#### 7.2.2.2. 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 open-label baseline at any open-label postbaseline visit up to and including the date of the last dose of open-label study drug + 3 day for those who discontinued open-label study drug permanently, or values that worsen by at least 3 grades from open-label baseline at any open-label postbaseline visit for those who are still on open-label study drug.

Post-treatment-emergent marked laboratory abnormalities will not be summarized for the TFFU phase.

#### 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) during the open-label phase:

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline (or open-label postbaseline, or post-TFFU baseline) value in the given study period. By-subject listings of Grade 3 or 4 and graded laboratory abnormalities will be provided by subject ID number and visit in chronological order.

### 7.2.3. ALT Flare and Exacerbation of Hepatitis

Summaries of the incidence of ALT flare and exacerbation of hepatitis will be provided by treatment group using the subjects in the Open-Label Safety Analysis Set for on-treatment occurrences during the open-label phase. On-treatment occurrences in the open-label phase will be defined as occurrences in the period between the first dose of open-labeled study drug to the last dose date of open-labeled study drug + 3 days. A supportive listing will also be generated.

Incidence of ALT flare and exacerbation of hepatitis is defined as:

- Serum ALT > 2 × study baseline and > 10 × ULN, with or without associated symptoms

OR

- Confirmed ALT elevation (defined as 1 grade shift [ie, increase] or 2 × previous value) with confirmed changes outside of the normal range in other laboratory parameters suggestive of worsening hepatic function (abnormal prothrombin time ≥ 2 seconds over study baseline or international normalized ratio [INR] ≥ 0.5 over study baseline, and abnormal serum albumin ≥ 1 g/dL below study baseline or elevated serum lactate levels [if available], defined as 2 × ULN).

If the first of two consecutive results is in the open-label phase and the second is out of the open-label phase, then the result will be considered to be confirmed in the open-label phase (assuming both values meet the criterion). And if the criterion is met by the last value in the open-label 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.

### 7.3. Bone Safety Analyses

For the Week 192 analysis, summaries of BMD-related analyses will be provided for both the double-blind and open-label phases based on the Spine and Whole Body DXA Analysis Sets and Open-label Spine and Whole Body DXA Analysis Sets. For open-label phase, open-label treatment of TDF and Placebo-TDF will be reported. Summaries of bone biomarker analyses will be provided based on the Safety Analysis Set and Open-Label Safety Analysis Set. Whole Body BMD measurements will exclude the head.

Change from open-label baseline for the open-label phase will be presented. There will be no p-value reported as subjects were not re-randomized during open-label phase.

#### 7.3.1. Bone Mineral Density (BMD)

Percent change from baseline in BMD of spine and whole body will be summarized by treatment group and visit up to Week 192. Percent change from baseline will be presented at each visit up to Week 192. In addition, BMD of spine and whole body at each visit and change from baseline will be summarized by treatment group.

The number and percentage subjects with percent change from baseline in spine and whole body BMD will also be summarized categorically by treatment group and visit using the following categories: ≤ 6%, > 6% to ≤ 4%, > 4% to ≤ -2%, > -2% to ≤ 0%, > 0% to ≤ 2%, >2% to ≤ 4%, >4% to ≤ 6%, > 6%, and Missing.

Spine and whole body Z-scores (derived from BMD assessment obtained via DXA scan) and changes in Z-scores from baseline will be summarized by treatment group and visit up to Week 192. Spine and whole body BMD clinical status will also be summarized categorically, and by categorical shift from baseline by treatment group using the following Z-score categories: > 1, 1 to 2, < 2, and Missing. The shift from baseline in Z-score categories will be summarized.

For categorical endpoints, percentages will be reported based on the number of non-missing measurements.

Mean (95% CIs) of the observed values for percentage change from baseline in spine and whole body BMD will be plotted by treatment group and across visits up to Week 192. Supportive listings will be provided for spine and whole body bone mineral density measurements, and for the subjects with at least 4% decline in spine and whole body bone mineral density.

### 7.3.2. Bone Biochemical Markers

Baseline, postbaseline, and change from baseline in bone biochemical markers, including urine bicarbonate, urine n-telopeptide, serum c-telopeptides, osteocalcin, bone specific alkaline phosphatase, PTH, vitamin D levels (25-hydroxy) and 1, 25 (dihydroxy vitamin) D levels, fasting serum creatinine and phosphate, spot urine creatinine and phosphate, and renal phosphate threshold (TmP/GFR) will be summarized by treatment group and visit. The change from baseline in bone biochemical markers will be presented. Supportive listings for bone biochemical marker measurements will also be provided. For fasting serum and fasting creatinine, only measurements taken when subject was confirmed to be fasting will be reported.

To calculate TmP/GFR, the following formula will be used based on serum creatinine and only for subjects confirmed to be fasting {Barth 2000}:

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

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

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

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

## 7.4. Renal Safety Analyses

### 7.4.1. Estimated Glomerular Filtration Rate (eGFR)

Glomerular filtration rate (estimated creatinine clearance) will be calculated using the Schwartz formula for subjects ages 2 to <18 as follows:

Schwartz formula (mL/min/1.73 $m^2$) k × L/Scr

k is a proportionality constant,

k 0.55 for pediatric males and females ≥ 2 years to < 12 years;

k 0.55 for adolescent females ≥ 12-18 years old; and

k 0.70 for adolescent males ≥ 12-18 years old

L is height in centimeters (cm); and

Scr is serum creatinine (mg/dL).

Summaries of eGFR and change from baseline in eGFR at baseline and at each postbaseline visit will be provided up to Week 192, including both the double-blind and open-label phases. Median (Q1, Q3) change from baseline in eGFR over time will be plotted.

Change from open-label baseline for the open-label phase will be presented. There will be no p-value reported.

### 7.4.2. Confirmed Renal Abnormalities

The following specific renal related laboratory abnormalities will be summarized up to Week 192:

- Confirmed (defined as 2 consecutive visits) increase in serum creatinine of ≥0.3 mg/dL above baseline
- Confirmed (defined as 2 consecutive visits) increase in serum creatinine of ≥0.5 mg/dL above study baseline
- Confirmed (defined as 2 consecutive visits) occurrence of serum phosphorus below 2.0 mg/dL
- Creatinine clearance by Schwartz formula ($CLcr_{Schwartz}$) < 50 mL/min
- $CLcr_{Schwartz}$ < 70 mL/min

If the first of two consecutive events occur, and the second is out of the open-label phase, then the result will be considered to be confirmed in the open-label phase (assuming both values meet the criterion). And if the criterion is met by the last value in the open-label 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.

## 7.5. Tanner Staging

Tanner Staging measurements will be summarized up to Week 192. The number and percentage of subjects with each Tanner Stage score (1-5) will be reported separately for females, including female pubic hair and female breast, and for males, including male pubic hair and male genitalia. The denominator used to calculate the percentage will be the number of female or male subjects using a M E approach, according to whether the measurement was for females or males.

## 7.6. Body Weight, Height and Vital Signs

Body weight (kg) and vital signs (blood pressure [mm Hg], respiratory rate [breaths/min], body temperature (◦C), and pulse [beats/min]) will be recorded at each scheduled time point.

Body weight, height, BMI, and corresponding Z-scores, and change from baseline will be summarized at each visit using descriptive statistics by treatment group. Z-scores for body weight, height, and BMI will be calculated using the LMS method based on CDC growth chart and reference method {Centers for Disease Control and Prevention (CDC) 2016}. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. Supportive listings for body weight, height, BMI and corresponding Z-scores, and vital signs will also be provided.

## 7.7. Prior Hepatitis B Medications

Prior HBV medications will be summarized using the number and percentage of subjects for each treatment group and overall using the Safety Analysis Set. Medications will be coded using the World Health Organization (WHO) Drug Dictionary. Each medication will be summarized by WHO Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically. No inferential statistics will be computed. A listing of prior HBV medications will also be provided.

## 7.8. Concomitant Medications

Concomitant medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary and summarized for the Open-Label Safety Analysis Set.

For the Week 192 analysis, summaries of concomitant medications using the number and percentage of subjects for each treatment group will be provided based for the Open-Label Safety Analysis Set by WHO ATC drug class Level 2 and preferred name. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. 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 the start or stop date will be used to determine if the medications are concomitant.

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

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

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

No inferential statistics will be provided. Subjects with any concomitant medication use will also be listed.

### 7.9. Electrocardiogram Results

This section is not applicable as electrocardiogram data were not collected.

### 7.10. Other Safety Measures

No other safety measure data were collected.

### 7.11. Changes From Protocol-Specified Safety Analyses

Baseline for BMD assessments for spine and whole body (via DXA scan) and serum bone biochemical markers will be calculated only using the Baseline Visit value, instead of taking the mean of the Screening and Baseline Visit values.

Treatment-emergent AEs and lab abnormalities were defined as any AE or lab abnormality that began on or after the study drug start date and no later than the study drug stop date in the protocol for those who discontinued study drug. This has been updated in this SAP to any AE with onset date on or after the open-label study drug start date and no later than the minimum of the open-label study drug stop date + 3 days for the open-label 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.

Centers for Disease Control and Prevention (CDC). Division of Nutrition, Physicial Activity, and Obesity> Nutrition: Growth Chart Training: A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). Available at: http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. 2016.

# 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.

# 10. SAP REVISION

| Revision Date (dd month, yyyy) | Section | Summary of Revision | Reason for Revision |
|---|---|---|---|
| Original (15 Oct 2020) | | | |
| | | | |

# 11. APPENDICES

## Appendix 1. Determining Missing and Virtual visits do to COVID-19

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If a visit which was to be conducted in-person was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Table 1) and "Virtual" (or synonyms, see Table 2). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

**STEP 1:** Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Table 2.

**STEP 2:** Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (Computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

i. If Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL 1, else COVIDFL 0
ii. If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL 1, else VIRTFL 0

**STEP 3:** For any comments with COVIDFL 1, assign "Missed visit" or "Virtual visit as follows

i. IF COVIDFL 1 and the visit date is missing then result is 'Missed Visit'
ii. IF COVIDFL 1 and VIRTFL 1 then result is 'Virtual Visit'
iii. Otherwise result is missing

**Table 1. Examples of search terms for "COVID-19" and "Virtual" used to identify missed and 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 |

**Table 2. Examples of extraneous text terms to eliminate from the comment fields**

| | | | | |
|---|---|---|---|---|
| a | down | in | she'd | until |
| about | during | into | she'll | up |
| above | each | is | she's | very |
| after | few | it | should | was |
| again | for | its | so | we |
| against | from | it's | some | we'd |
| all | further | itself | such | we'll |
| am | had | i've | than | were |
| an | has | let's | that | we're |
| and | have | me | that's | we've |
| any | having | more | the | what |
| are | he | most | their | what's |
| as | he'd | my | theirs | when |
| at | he'll | myself | them | when's |
| be | her | nor | themselves | where |
| because | here | of | then | where's |
| been | here's | on | there | which |
| before | hers | once | there's | while |
| being | herself | only | these | who |
| below | he's | or | they | whom |
| between | him | other | they'd | who's |
| both | himself | ought | they'll | why |
| but | his | our | they're | why's |
| by | how | ours | they've | with |
| could | how's | ourselves | this | would |
| did | i | out | those | you |
| do | i'd | over | through | you'd |
| does | if | own | to | you'll |
| doing | i'll | same | too | your |
| down | i'm | she | under | you're |
| | you've | yourself | yourselves | yours |

# GS-US-174-0144 SAP W192

# ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | Biostatistics eSigned | 15-Oct-2020 22:42:41 |
| PPD | Clinical Research eSigned | 15-Oct-2020 23:03:10 |
| PPD | Regulatory Affairs eSigned | 16-Oct-2020 16:24:37 |