STATISTICAL ANALYSIS PLAN

Study Title:	Pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate (TDF, Viread®) and describe the management of TDF-associated renal and bone toxicity in Chronic Hepatitis B (CHB)-infected adolescents aged 12 to <18 years in Europe
Name of Test Drug:	Tenofovir disproxil fumarate
Study Number:	GS-EU-174-1403
Protocol Version:	Amendment 2
Protocol Date:	10MAR2015
Analysis Type:	End of Study (Early Termination)
Analysis Plan Version:	Final 1.0
Analysis Plan Date:	13 May 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BL	Baseline
BMD	Bone mineral density
BMI	Body mass index
BPM	Beats per minute
CBC	Complete blood count
CHB	Chronic hepatitis B
CK	Creatine kinase
CRF	Case report form
CRO	Contract research organization
DAVG	Difference between time-weighted average post-baseline and baseline
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPFV	First patient first visit
GGT	Gamma glutamyl transferase
HBV	Hepatitis B virus
HLT	High level term
HLGT	High level group term
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LLT	Lower level term
LLQ	Lower limit of quantification
LPLV	Last patient last visit
MedDRA	Medical dictionary for regulatory activities
OL	Open label
PCR	Polymerase chain reaction
PT	Prothrombin time
PTH	Parathyroid hormone
PK	Pharmacokinetics
PP	Per protocol

PT	Preferred term
Q1	First quartile
Q3	Third quartile
QTc	Corrected QT
QTcB	Corrected QT (Bazett's formula)
QTcF	Corrected QT (Fridericia's formula)
RAS	Randomized analysis set
SADR	Serious adverse drug reaction
SAP	Statistical analysis plan
SOC	System organ class
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
TFLs	Tables, figures, and listings
WHO	World Health Organization

1. INTRODUCTION

This was a post-authorization randomized open-label study comparing the bone and renal safety profiles of adolescents (12-17 years, inclusive) with chronic hepatitis B (CHB) infection. The study assigns patients receiving TDF 245mg by mouth (per os[PO]) once daily for the treatment of CHB to one of two schedules for bone and renal laboratory monitoring and bone mineral density (BMD) measurements over 96 weeks. The study population was enrolled through one of the 23 participating European clinics (ie., Belgium, Romania, Spain, Bulgaria, France, Italy, Greece, and the United Kingdom) and FPFV was in July 2015.

The scope of this statistical analysis plan (SAP) is for the final analysis (Week 96).

1.1. Study Objectives

Primary Study Objectives	To characterize the long term (i.e., 96 weeks of follow up) bone safety profile of open-label TDF treatment in adolescents with CHB. This includes prospectively evaluating and comparing the bone mineral density (BMD) changes between CHB- infected adolescents 12 to < 18 years of age treated with TDF in European treatment centers who were assigned to one of two schedules for renal and bone laboratory monitoring and BMD measurements. Primary study endpoint was the percent changes in BMD from Baseline through study Week 96.
Secondary Study Objectives	• To document all serious adverse drug reactions (SADR) and all renal- and bone-related adverse events (AEs), including renal and bone laboratory abnormalities • To determine the time to diagnosis of renal and bone AEs and document the resulting patient management and outcome(s) • To assess the clinical management and outcomes of renal- and bone-related ≥ Grade 3 laboratory parameters and clinical SAEs. • To assess the efficacy and tolerability of TDF in adolescents with CHB infection • To assess the use of oral vitamin D, calcium and phosphate supplementation and explore the association between supplement use and rates of bone and renal AEs • To describe the demographics and disease characteristics of adolescents with CHB infection treated with TDF.

1.2. Study Design

Design Configuration and Subject Population	This study is a post-authorization, randomized open-label study comprised of adolescents who initiate 245mg PO once daily tTDF therapy for the treatment of HBV in clinical sites across Europe. The subjects will be assigned in a 1:1 ratio to one of two monitoring groups using a validated computer-generated tool for randomization. Subjects will be assigned to Group 1 or 2 upon enrollment into the study but prior to Baseline laboratory and DXA imaging assessments.
Treatment Groups	**Monitoring Group 1** will receive tTDF 245mg PO once daily for the treatment of CHB infection, followed over 96 weeks using an enhanced monitoring protocol which includes more frequent laboratory bone biomarker testing and lumbar spine and whole-body DXA scans (Baseline, and Weeks 24, 48, 72, 96) than that which is specified for Group 2. With the exception of an enhanced monitoring protocol for bone and renal outcomes, subjects will be managed according to local standards of care. **Monitoring Group 2** will be the comparator group of subjects receiving tTDF 245mg PO once daily for the treatment of CHB infection, and with the exception of pre-specified bone monitoring, will be managed according to local standards of care. Group 2 will receive serum bone biomarker testing, and lumbar spine and whole body DXA at Baseline, Weeks 48 and 96.
Key Eligibility Criteria	**Inclusion Criteria** • Subjects must meet all inclusion criteria as stated in the protocol to be eligible for participation in this study. These include: — 12 to <16 years of age — Documented chronic HBV infection (e.g. positive serum HBsAg≥ 6 months) — Weight ≥ 35 kg — Able to swallow oral tablets — Negative serum β-HCG pregnancy test — Estimated glomerular filtration rate (creatinine clearance) ≥ 80 mL/min/1.73m^2

	Estimated creatinine clearance using Schwartz Formula: (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant: for adolescent females ≥ 12 years old, k = 0.55, and for adolescent males ≥ 12 years, k = 0.70); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)] Parent or legal guardian of potential study subjects able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements or subject able to provide written assent as determined by IEC/local requirements and at the Investigator's discretion.
Key Eligibility Criteria	**Exclusion Criteria** Prior therapy with tTDF; subjects may have received prior interferon or oral anti-HBV nucleoside/nucleotide therapy (subjects experienced on interferon must have discontinued therapy for a minimum of six months; treatment-experienced subjects receiving oral anti-HBV nucleoside/ nucleotide treatment at screening should continue their current treatment regimen until tTDF is initiated (i.e., to prevent ALT flare) Sexually-active males or females of reproductive potential who are not willing to use an effective method of contraception during the study. Females who are pregnant or breastfeeding, or females who wish to become pregnant during the course of the study. Known hypersensitivity to tTDF, the metabolites or formulation excipients Any condition (including alcohol or substance abuse) or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with treatment requirements
Study Periods/Phases	Screening period = 30 days Total treatment period = 96 weeks

Randomization, Blinding, and Unblinding	• 30 TDF-naïve subjects were randomized in a 1:1 ratio to receive tTDF 245mg PO daily and assigned to one of two safety monitoring groups (15 subjects each). • Randomization was not stratified by age or region. A centralized randomization procedure was used, whereby numbered bottles of TDF are assigned to subjects via an interactive voice response system (IVRS) according to the randomization code.
Study Duration	Subjects will be treated with TDF for 96 weeks. The duration for a given subject is at least 96 weeks plus 30 days to observe safety outcomes. Subjects who permanently discontinue TDF will be asked to return for an end-of-treatment visit within 72 hours of the last dose of TDF. Subjects who permanently discontinue TDF will be followed for 24 weeks off treatment or up to initiation of active treatment, whichever occurs first.

1.3. End of Study

The end of study is defined as the completion of TDF therapy and close-out monitoring by the last enrolled subject (e.g., last enrolled subject completes 96 Weeks of treatment and monitoring).

Randomization	Approximately 100 TDF-naive patients were planned to be randomized in a 1:1 ratio to receive treatment with TDF and assigned to one of two monitoring groups (50 in each group was planned). The subjects were assigned to one of two monitoring groups using a validated computer-generated tool for randomization (dynamic block assignment by site to ensure there are at least 4 subjects randomized per site). Subjects were assigned to Group 1 or 2 upon enrollment into the study but prior to Baseline laboratory and DXA imaging assessments. The study population was enrolled through one of 23 participating European clinics across several countries (eg., Bulgaria, Poland, Romania, Italy, France, Spain, and the United Kingdom) commencing June 2015

Site and/or Stratum Enrollment Limits	There were no enrollment limits imposed at the sites.
Study Duration	Subjects will be treated with TDF for 96 weeks. The planned duration in-study for a given subject is at least 2 years. TDF is currently approved for use in patients across all specified study countries with participating study clinics aged 12 years of age and up. Subjects who permanently discontinue TDF will be asked to return for an end-of-treatment visit within 72 hours of the last dose of TDF. Subjects who permanently discontinue TDF will be followed for 24 weeks off treatment or up to initiation of active treatment, whichever occurs first.

1.4. Sample Size and Power

Planned Sample Size	100 subjects (50 subjects to one of two monitoring groups)
Power Statement	The study employed two monitoring protocols which specified the same laboratory and imaging tests for bone and renal markers and differed in the frequency of testing. Group 1 receives more frequent monitoring which is protocol-defined or SmPC specified, and Group 2 subjects are monitored according to a less frequent DXA schedule for BMD and followed the local standard of care for renal monitoring. It is hypothesized (H_0) that there would have been no difference in the timing, management, or subject outcomes resulting from renal or bone AEs among the two monitoring regimens. With a one-tailed test of α=0.05, and assuming a non-inferiority margin of 0.10, the study had at least 80% power to detect a difference between the monitoring regimens beyond the specified margin of non-inferiority. The primary safety endpoint is cumulative incidence of at least a 4% decrease from study baseline (BL) in spine bone mineral density (BMD) through Week 96. The null hypothesis is the difference (Group 1 – Group 2) is equal to 0. The alternative hypothesis is the difference (Group 1 – Group 2) is not equal to 0.

Actual Enrollment and Impact on Power	The study failed to achieve its targeted enrollment of 100 patients, 50 per monitoring group. The study was discontinued as a result of the recent approval of Tenofovir alafenamide fumarate (TAF) medicine which offers a safer treatment option for CHB patients and due to low subject enrollment after the CHMPs assessment of the 18 month interim enrollment report. At the time of its closure the study enrolled 30 patients, 15 per monitoring group. The total enrolled subjects are underpowered to statistically detect differences in outcomes between monitoring groups.

2. TYPE OF PLANNED ANALYSIS

2.1. Final Analysis

Final Analysis includes the time period from the first date of OL TDF dose through and including the date of last OL TDF dose plus 30 days. As a result of early study termination (FPFV July 2015 to LPLV April 2018) only two patients completed 96 weeks of observation on TDF treatment for HBV, the primary study objective to characterize the safety profile (renal and bone adverse outcomes) of subjects will be summarized based on available TDF exposure time. The assessment of efficacy and tolerability of TDF will be described. As most of the enrolled subjects were unable to complete the target observation period of 96 weeks, the final analysis will be unable to provide meaningful evidence to suggest whether enhanced or standard of care renal and bone monitoring frequencies between Group 1 and Group 2 offer early detection and mitigation of renal or bone adverse events. Instead, the data will be described by monitoring group and pooled together where possible.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. Per International Conference on Harmonisation (ICH) E9, the intention-to-treat principle implies that the primary analysis should include all randomized subjects. It is recognized, however, that the ideal of complete follow-up of all randomized subjects is difficult to achieve. Therefore, the term "full analysis set (FAS)" will be used to identify the analysis set that is considered as close as possible to the intention-to-treat ideal of all randomized subjects.

The assignment of subjects to analysis sets will be done before the study blind is broken for analysis. A summary of the number and percentage of subjects in each analysis set will be provided by monitoring group and in total.

3.1.1. Randomized

The Randomized analysis set (RAS) includes subjects who were randomized into the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes subjects who were randomized into the study and received at least one dose of TDF.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes subjects who were randomized into the study and received at least one dose of TDF. For this study there is no functional difference between FAS and the Safety Analysis Set.

3.1.4. Pharmacokinetics

Not applicable

3.2. Subject Groups

Subjects will be grouped for analyses according to randomized treatment for efficacy analysis using FAS. Subjects will be grouped according to actual treatment received for safety analysis using safety analysis set.

Unless otherwise specified, safety data will be summarized in tables by monitoring group as follows:

Group 1 – enhanced monitoring group, TDF

Group 2 – standard of care monitoring group, TDF

Pooled - All TDF

3.3. Strata and Covariates

Randomization was not stratified by age or region

3.4. Examination of Subject Subsets

Subgroup analyses were to be performed for the following secondary efficacy endpoints:

- Proportion with HBV DNA < 400 copies/mL (<69 IU/mL)
- Proportion with HBsAg loss

Subgroup analyses were to be performed for the following secondary safety endpoints:

- Subjects receiving dietary supplementation (e.g., Vitamin D, calcium, or phosphate)

3.5. Multiple Comparisons

No interim analysis of efficacy data will be performed prior to the Week 96 end of treatment analysis. Therefore no adjustment to the alpha level is required for this study.

3.6. Missing Data and Outliers

Missing Data

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. Sensitivity analyses will be performed if warranted.

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window.

Outliers

No special handling of outliers will be employed.

3.7. Data Handling Conventions and Transformations

HBV DNA levels will be measured using the Roche COBAS Taqman 48 assay, and values below the lower limit of quantitation (LLQ) for the assay will be set to the lower limit minus 1 (168 copies/mL [28 IU/mL]) for calculation of summary statistics for the actual HBV DNA values, change from study BL values by study visit. The original values will be provided in the HBV DNA listing.

For selected analyses, HBV DNA data (in copies/mL) will be transformed to the logarithmic (base 10) scale (log_{10} copies/mL).

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

- HBsAg and HBeAg borderline will be considered as HBsAg positive and HBeAg positive.
- HBsAb and HBeAb borderline will be considered as HBsAb negative and HBeAb negative.

For the determination of summary and order statistics, safety laboratory data that are continuous in nature but below the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned). Individual values that include symbols "<" or ">" will be presented as "<" or ">" in the data listings.

3.8. Visit Windows

3.8.1. Definition of Study Day 1

Study Day 1 is defined as the date of study baseline (BL). Study BL is defined as the first dose date of TDF. If the first dose of TDF date is missing, then it will be estimated by using the baseline visit date. In the event that data are missing for an endpoint at study BL, the last non-missing data collected prior to this study BL date will be used as study BL measurement. For subjects who have more than one value on the same study BL visit date, the mean (arithmetic or geometric, as appropriate) value will be used as the study BL value for continuous data, while the latest pre-dose value will be used as the study BL value for categorical data. For subjects who have more than one study BL value with different visit dates, the last value on or prior to the first dose date of TDF will be used as study BL.

3.8.2. Analysis Windows

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

Table 3-1. Windows of Time Relative to Study BL Used to Classify Subject Assessments (except DXA, Bone Biochemical Markers and Serology)

Period	Nominal Day	Lowest	Highest
Study BL[a]	1		1
Week 4	28	2	42
Week 12	84	43	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Follow-up Week 24		Last dose date + 155	Last dose date + 182

DXA, BMD, and serum bone biochemical markers data require special consideration, as they are collected infrequently, only at study BL and Weeks 24, 48, 72, and 96 (bone markers data are also collected at the screening visit). Randomization cannot occur until after the BL (pretreatment) DXA scan has been performed. As such, the windowing conventions depicted in Table 3-2 will be used for DXA BMD data.

Table 3-2. DXA BMD and Bone Biochemical Markers Data Windows of Time Relative to Study BL Used to Classify Subject Assessments for Week 96 Analyses

Period	Nominal Day	Lowest	Highest
Study BL[a]	1		1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756

a Study day computed from first dose date of TDF.

Windowing conventions to be used for serology data relative to study baseline are depicted in Table 3-3.

Table 3-3. Serology Data Windows of Time Relative to Study BL Used to Classify Subject Assessments

Period	Nominal Day	Lowest	Highest
Study BL	1		1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756 *

a Study day computed from first dose date of TDF.

3.8.3. Selection of Data in the Event of Multiple Records in a Window

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

Serology

In the event that 2 or more serology results (eg, HBeAg and anti-HBe or HBsAg and anti-HBs) occur within the same visit window, then the pair will remain together and the last pair of results in the window will be used for analysis purposes.

ALT

The highest value will be included in the analysis when 2 or more ALT values occur within the same visit window.

HBV DNA values (log_{10} copies/mL)

1) Select the record closest to the nominal day (eg, Day 168 for analysis Week 24) for that visit.

2) If there are 2 visits equidistant from the nominal day, take the latest.

3) If there are multiple records on a selected day, take the geometric mean. If there are 2 values on the same day and it can be determined that the second one is a retest because there was a problem with the first test (for example, specimen hemolyzed), in these cases, the later value should be used.

All other laboratory parameters, DXA data, height, weight, and BMI

1) Select the record closest to the nominal day (eg, Day 168 for analysis Week 24) for that visit.

2) If there are 2 visits equidistant from the nominal day, take the latest.

3) For continuous variables, if there are multiple records on a selected day, take the arithmetic mean. For laboratory parameters, if there are 2 values on the same day and it can be determined that the second is a retest because there was a problem with the first test (for example, specimen hemolyzed), then the later value will be used. For categorical variables, if there are multiple records on a selected day, take the later value.

3.9. Handling Missing Data in Evaluation of Efficacy

3.9.1. Missing = Excluded Analysis

The primary method of handling missing data in evaluation of efficacy is the missing = excluded (M = E) approach. Due to the ad-hoc nature visits and tests within study group 2, M=E is preferred.

3.9.2. Missing = Failure Analysis

An alternative to the M = E approach is the missing = excluded (M = F) approach.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects screened (without percentage), randomized, randomized and treated with TDF, randomized and treated with TDF for all countries combined and by country and investigator site will be summarized by monitoring group and overall. Similarly, the number and percentage of subjects randomized into each age group (12-14 years, 15–16 years) and geographic region (by EU members) will be summarized. The denominator for this calculation will be the number of subjects in the Randomized Analysis Set.

4.2. Disposition of Subjects

A summary of subject disposition will be provided by monitoring group and overall. This summary will present the number of subjects screened, randomized, included in the safety analysis set, and the number and percentage of subjects meeting the following criteria:

- Completed the study treatment period,
- Did not complete the study treatment period (with summary of reasons for not completing the study treatment period),
- Completed the study (includes the study treatment period), and
- Did not complete the study (with summary of reasons for not completing the study).

The denominator for the percentages of subjects in each category will be the number of subjects in the Safety Analysis set.

No inferential statistics will be generated. A data listing of reasons for premature study treatment/study discontinuation will be provided. The most recent, non-missing primary and key secondary endpoint values prior to discontinuation will be included in this listing.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to TDF

Duration of exposure to TDF will be defined as (last dose date – first dose date + 1)/7, regardless of temporary interruptions in TDF administration, and will be expressed in weeks (recorded to one decimal place, e.g., 4.5 weeks). Duration of exposure to TDF will be summarized using descriptive statistics (sample size, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum) and as the number and percentage of subjects with data in a given analysis window (using the analysis windows defined in Section 3.8.2) by monitoring group and overall for the Safety Analysis set. No inferential statistics will be computed.

4.3.2. Adherence with TDF

Descriptive statistics for adherence (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) along with the number and percentage of subjects belonging to adherence categories (e.g., < 80%, ≥ 80 to < 90%, ≥ 90%) will be provided by monitoring group for the safety analysis set. No inferential statistics will be provided.

For the Final Analyses:

Adherence (%) with TDF during the treatment period will be calculated as where

$$\text{Adherence (\%)} = 100 \times \frac{\sum \text{Number of tablets taken at each distinct dispensed period [1]}}{\sum \text{Number of tablets prescribed at each distinct dispensed period [2]}}$$

[1] Number of tablets taken at each distinct dispensed period is calculated as the minimum of [the daily number of pills prescribed multiplied by the duration of treatment* at each dispensed period of the same dispensed date, and (number of pills dispensed minus the number of pills returned)].

[2] Number of pills prescribed at each distinct dispensed period is calculated as the daily number of pills prescribed multiplied by the duration of treatment* at each dispensed period of the same dispensed date.

* The duration of treatment at each dispensed date is calculated as the minimum of (the last returned date of the same dispensed period, date of last pill of permanent discontinuation of study regimen, and next pill dispensed date) minus dispensed date.

The next pill dispensed date is the following dispensed date of the same drug, including the TDF bottle not returned.

Adherence will be calculated and summarized for each subject for the entire dosing period up to the date of permanent discontinuation of the study regimen.

For a record where the number of pills returned is missing, it is assumed the number of pills returned is 0. If the number of pills dispensed is missing, then all records for the same dispensed date will be excluded from both denominator and numerator calculation.

If any TDF bottle is not returned for the same dispensed date, then all of the records for the dispensed date will be excluded from both denominator and numerator calculation.

In case of any additional bottles dispensed to cover a longer than protocol-specified-visit period, these extra bottles will be counted in the calculation.

Adherence will be calculated and summarized for TDF tablets for each subject for the entire dosing period. Treatment interruptions approved by the investigator are not considered to be non-adherence.

Descriptive statistics for adherence (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 90%, ≥ 90%) will be provided by monitoring group and overall. No inferential statistics will be computed.

4.4. Protocol Deviations

A listing will be provided of subjects in the safety analysis set who violated at least one inclusion or exclusion criteria. The listing will include the criteria not met and related comments.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Demographic summaries will include gender, race, ethnic origin, age, geographic region, and randomization age group (12–14 years, 15–17 years) and geographical location (European Union member states).

Study BL characteristic summaries will include body weight (kg), height (cm), BMI (kg/m^2), and HBV genotype.

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be summarized for continuous data and the number and percent of subjects will be summarized for categorical data.

Age is calculated as age in years at first dose of TDF and will be calculated using the following SAS code:

```
age2 = int(yrdif(birthdt, fdosedt, 'AGE'));
```

No inferential statistics will be computed. Data listings for demographics and BL characteristics will be provided using the Safety Analysis Set.

5.2. Baseline Disease Characteristics

Study BL disease characteristic summaries will include log_{10} (HBV DNA [copies/mL]) level, HBV serology, ALT value ([U/L] including normal versus abnormal), AST value (U/L), number of years with HBV, number of years since first HBV treatment, spine and whole-body BMD ($[g/cm^2]$ via DXA scan), and serum bone biochemical markers (see Section 6.6).

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be summarized for continuous data and the number and percent of subjects will be summarized for categorical data. Number of years with HBV and HBV treatment will be calculated from study BL.

5.3. Medical History

Disease-specific medical history will be collected on the CRF and will be summarized by monitoring group and overall by the number and percentage of subjects with each condition.

General medical history (i.e., conditions not specific to the disease being studied) data will be listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Definition of the Primary Efficacy Endpoint

An efficacy analysis would be conducted after the last assigned subject completes Week 96 of TDF treatment for CHB. As the study has been prematurely discontinued, a descriptive analysis will be performed to outline the subjects who completed 96 weeks of treatment and review the HBV DNA results for subjects at their early discontinuation visit as part of study closeout proceedings.

The planned analysis will evaluate the difference in the proportion of subjects (Group 1 and 2 data will be analyzed separately and pooled as subjects have exposure to a single mode of therapy) achieving a composite endpoint of HBV DNA <400 copies/mL and ALT normal at Week 96, using a two-sided Fisher exact test with a non-completer equals excluded approach.

6.2. Statistical Hypothesis for the Primary Efficacy Endpoint

H_0: The difference between Monitoring Groups 1 and 2 in the proportions of subjects with HBV DNA <400 copies/mL at Week 96 is equal to 0

H_1: The difference between Monitoring Groups 1 and 2 in the proportions of subjects with HBV DNA <400 copies/mL at Week 96 is not equal to 0

6.3. Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will be conducted at the end of the study period, after the last randomized subject reaches Week 96, using the FAS. The analysis will evaluate the difference between monitoring groups in the proportion of subjects achieving the primary endpoint, using a Mantel-Haenszel test. As the study was prematurely discontinued, a descriptive analysis of subjects who met a composite endpoint of HBV DNA <400 copies/mL and ALT normal at Week 96 or at their early discontinuation visit will be reported.

6.4. Secondary Efficacy Endpoints

No secondary efficacy endpoints are planned.

6.5. Exploratory Efficacy Endpoints

PPD

6.6. Changes From Protocol-Specified Efficacy Analyses

None

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

AEs are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the 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 TDF

Related AEs are those for which the investigator answers "Yes" to the question "Is there a reasonable possibility that the study treatment caused or contributed to the adverse event?" Events for which the investigator did not record relationship to TDF will be considered related to TDF. Data listings will show relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent AEs are events in a given study period that meet one of the following criteria:

- Began on or after the date of the first dose of TDF and on or before the date of the last dose of TDF plus 30 days
- Had no recorded start date and the stop date is not before the first dose of TDF.

Exception: An event with an onset on the same or next calendar day that a previous event resolves is not treatment emergent if all of the following criteria are met:

- The events have the same MedDRA Lower Level Term
- The later event has the same or lower severity grade
- The later event is not related to TDF

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine treatment emergent as follows. The event is treatment emergent if the month and year of onset (or year of onset) of the event meets both of the following criteria:

- The same as or after the month and year (or year) of the first dose of TDF
- The same as or before the month and year (or year) of the 7th day after the last dose of TDF

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, by monitoring group, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any Grade 3 or 4 treatment-emergent AE, (3) had any Grade 2, 3 or 4 treatment-emergent AE, (4) had any treatment-emergent treatment-related AE, (5) had any Grade 3 or 4 treatment-emergent treatment-related AE, (6) had any Grade 2, 3 or 4 treatment-emergent treatment-related AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent treatment-related SAE, (9) permanently discontinued from TDF due to an AE, and (10) died during study.

Summaries (number and percentage of subjects) of adverse events (by SOC and PT) will be provided by monitoring group using the safety analysis set as follows:

- All treatment-emergent bone or renal AEs
- All TDF-related treatment-emergent bone or renal AEs
- Combined Grade 3 and 4 treatment-emergent bone or renal AEs
- Combined Grade 2, 3 and 4 treatment-emergent bone or renal AEs
- Combined Grade 3 and 4 treatment-emergent treatment-related bone or renal AEs
- Combined Grade 2, 3 and 4 treatment-emergent treatment-related bone or renal AEs
- All treatment-emergent serious AEs
- All treatment-emergent treatment-related SAEs

- All treatment-emergent AEs that caused permanent discontinuation from TDF
- All treatment-emergent AEs that caused change in dose or temporary interruption of TDF
- Deaths
- All AEs recorded between screening and first dose of TDF

For final analyses, summaries will be provided by monitoring group and overall TDF.

Summaries and data listings will use the Safety Analysis Set.

Events will be summarized based on the date of onset for the event, according to the definition of treatment emergent in Section 7.1.5. Non-treatment emergent events, including those prior to the first dose date of TDF, will be included in data listings.

Multiple events will be counted once only per subject in each summary. For data presentation, SOC 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-monitoring group summaries, data listings will be provided for the following:

- All AEs (with a variable indicating whether the event is treatment-emergent)
- SAEs (including deaths)
- AEs leading to discontinuation of TDF
- Subjects experiencing pregnancy during the study

PPD

7.1.7. Additional Analysis of Adverse Events

PPD

7.2. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized by the observed data and change over time. Missing laboratory results for safety summaries will not be imputed. In all cases for laboratory evaluations, no inferential statistics will be computed.

Glomerular filtration rate (estimated creatinine clearance) will be calculated via statistical programming at each visit

(a) using Schwartz formula for subjects ages 12–18 years (ie, 12 to < 19) as follows:

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

k is a proportionality constant,

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)

(b) using Cockcroft-Gault equation for age ≥ 12 years as follows:

$$\frac{(140 - \text{age in years})\ (\text{body weight [kg]})}{(72)\ (\text{serum creatinine [mg/dl]})}$$

[Note: multiply estimated rate by 0.85 for women; use actual body weight]

Creatinine clearance (CLcr) summaries will be provided by Schwartz and Cockcroft-Gault separately.

Summaries and data listings will use the Safety Analysis Set. For subjects who discontinue prior to the final week for the given analysis, all on-treatment laboratory data collected on or before the date of last dose + 7 days will be included in tabular summaries. Laboratory data prior to the first dose date of TDF will be included in data listings.

Summaries of laboratory data will be provided for the safety analysis set. No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by monitoring group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline analysis window
- Change from baseline at each post-baseline analysis window

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 *Selection of Data in the Event of Multiple Records in a Window*. Laboratory data collected prior to the first dose date of TDF will be included in data listings.

7.2.2. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially life threatening (Grade 4). 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; analyses for each direction (i.e., increased, decreased) will be presented separately. Grading of laboratory abnormalities for analysis purposes will be performed by the central laboratory.

Laboratory abnormalities may be reported as an AE, and the clinical grading of an event may be different from the quantitative grading depending on the clinical status and underlying conditions.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least one toxicity grade from baseline at any time post-baseline up to and including the date of last dose of TDF plus 30 days. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

Treatment-emergent laboratory abnormalities and Grade 3 or 4 treatment-emergent laboratory abnormalities by monitoring group and overall will be summarized based on the date of the abnormality. Abnormalities that occur prior to the first dose date of TDF or during follow-up will be included only in data listings.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that worsen from baseline by at least 3 grades at any post-baseline, on-treatment value. On-treatment values include those up to and including the date of the last dose of TDF plus 30 days. If the relevant baseline laboratory data are missing, then any Grade 3 or 4 on-treatment values will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities will be provided by monitoring group (subjects categorized according to most severe abnormality grade), where applicable:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values in the given study period. A listing of treatment-emergent Grade 3 or Grade 4 laboratory abnormalities will be provided.

Incidence of ALT flare and post-treatment exacerbation of hepatitis is defined as follows:

- Serum ALT > 2 × study BL 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 (total bilirubin ≥ 2 mg/dL above study BL, abnormal prothrombin time ≥ 2 seconds over BL or international normalized ratio [INR] ≥ 0.5 over BL, abnormal serum albumin ≥ 1 g/dL below BL or elevated serum lactate levels [if available], defined as 2 × ULN).

Summaries (number and percentage of subjects) of treatment-emergent, on-treatment laboratory abnormalities will be provided by monitoring group and overall, with the following modifications for the creatinine summaries:

Confirmed (defined as 2 consecutive visits) increase in serum creatinine of 0.3 mg/dL above BL

Confirmed (defined as 2 consecutive visits) increase in serum creatinine of 0.5 mg/dL above BL.

A confirmed laboratory results is defined as either being present at 2 consecutive visits or at the last visit. If the first of 2 consecutive results is on-treatment and the second is off-treatment, then the result is considered confirmed.

For all summaries of laboratory abnormalities, the denominator is the number of subjects in the Safety Analysis Set.

Hepatic flares will be summarized by monitoring group and overall.

7.3. Bone Mineral Density and Bone Biochemical Markers

BMD primary endpoints to be evaluated include:

- Cumulative incidence of at least a 4% decrease from baseline in spine BMD
- Spine BMD (g/cm^2) and change from baseline
- Percent change from baseline in spine BMD (categorical)
- Z-Scores for spine BMD (g/cm^2) and change from baseline (categorical)
- Cumulative incidence of at least a 4% decrease from baseline in whole-body BMD
- Whole-body BMD (g/cm^2) and change from baseline
- Percent change from Baseline in whole-body BMD (categorical)
- Z-Scores for whole-body BMD (g/cm^2) and change from baseline (Categorical)

Cumulative incidence of at least a 4% decrease from BL in spine and whole-body BMD will be summarized by monitoring group and study week for each randomization age group (12-14 years, 15–17 years). No inferential statistics will be computed.

The percent change from BL in spine BMD and in whole-body BMD will also be summarized categorically by monitoring group and overall for each study week using the following categories: ≤–4, >–4 to ≤–2, >–2 to ≤0, >0 to ≤2, >2 to ≤4, >4, and Missing. No inferential statistics will be computed.

Z-score and changes from BL in z-score will also be summarized categorically (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) by monitoring group and overall for each study week. No inferential statistics will be computed.

Spine BMD and whole-body BMD clinical status will also be summarized categorically by monitoring group and overall for each study week using the following categories: >-1, -1 to -2, <-2, Total, and Missing. No inferential statistics will be computed.

Serum bone biochemical markers will be summarized (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) by monitoring group and overall for each study week, as well as the changes from BL. In all cases of serum bone biochemical markers, no inferential statistics will be computed.

The following bone biochemical markers as previously mentioned in the laboratory results section will be assessed:

- N-telopeptide (nmol BCE/L)
- C-telopeptide (ng/mL)
- Serum osteocalcin (ng/mL)

- Bone-specific alkaline phosphatase (µg/L)
- Serum PTH (pg/mL)
- Vitamin D (25-hydroxy, [ng/mL])

Baseline, and change from baseline in bone biochemical markers will be summarized by treatment group and visit using the Safety Analysis Set. The change from baseline in bone biochemical markers will be compared using the Wilcoxon rank-sum test up to Week 48, where applicable. 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.

7.4. Body Weight and Vital Signs

Body weight at each visit, and change from baseline in body weight will be summarized for the safety analysis set using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) by monitoring group for each post BL analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 *Selection of Data in the Event of Multiple Records in a Window*. No inferential statistics will be generated.

Vital signs will be provided in data listings for the Safety Analysis Set. Abnormal vital signs values will be identified with an asterisk.

Table 7-1. Flagging Threshold Criteria

Vital Sign	Flagging Threshold
Systolic Blood Pressure	< 90 mmHg and a decrease of ≥ 20 mmHg from study BL, or > 150 mmHg and an increase of ≥ 20 mmHg from study BL
Diastolic Blood Pressure	< 50 mmHg and a decrease of ≥ 15 mmHg from study BL, or > 105 mmHg and an increase of ≥ 15 mmHg from study BL
Pulse	< 50 bpm and a decrease of ≥ 15 bpm from study BL, or > 120 bpm and an increase of ≥ 15 bpm from study BL

Z-scores for height, weight and BMI will be summarized by monitoring group and overall, using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum), at BL and for each post-BL analysis window by study week, along with their respective changes from BL. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Height, weight, and BMI, and their corresponding z-scores, will be provided in data listings for the Safety Analysis Set. No inferential statistics will be computed. Z-scores for body weight, height, and BMI will be calculated using US Centers for Disease Control and Prevention growth charts.

7.5. Prior Hepatitis B Medications

Medications used in the treatment of CHB prior to the study will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of CHB medications before the start of study will be summarized (number and percentage of subjects) by monitoring group and WHO preferred name. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be ordered by decreasing total frequency of use.

Summaries of prior CHB medications will be provided for the safety analysis set. No inferential statistics will be generated.

7.6. Concomitant Medications

Concomitant medications (i.e., medications other than TDF that are taken while receiving TDF) will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications up to and including the date of last dose of TDF plus 30 days will be summarized (number and percentage of subjects) by monitoring group, WHO drug class, and WHO generic name. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class.

Summaries of concomitant medications will be provided for the safety analysis set. No inferential statistics will be generated.

7.7. Other Safety Measures

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

7.8. Changes From Protocol-Specified Safety Analyses

No alterations to the protocol-specified safety analysis have been made. The study has been canceled due to low enrolment and due to the approval of TAF for HBV in adolescents in November 2016 as a safer treatment option for patients. With two subjects completing 96 weeks of treatment the safety analysis will shift to focus on subjects' available treatment exposure to TDF.

8. PHARMACOKINETIC ANALYSES

Not applicable

9. REFERENCES

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. 2018.

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63 (1):261-83.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. **Study Procedures Table**

Appendix 2. **GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities**

Appendix 3. **Table of Contents for Statistical Tables, Figures, and Listings**

Appendix 1. Study Procedures Table

Study Procedures	Screening	Baseline	Study Week									30d Follow-Up
			4	12	24	36	48	60	72	84	96	
Written Informed Consent	x											
Medical History	x											
HBV DNA		x		x	x	x	x	x	x	x	x	
HBV serology	x	x			x		x		x		x	
HCV, HDV, HIV screening		x										
HBV genotype		x										
DXA, Group 1		x			x		x		x		x	
DXA, Group 2		x					x				x	
Serum bone chemistry, Group 1		x			x		x		x		x	
Serum bone chemistry, Group 2		x					x				x	
Serum renal chemistry, Group 1	x	x	x	x	x	x	x	x	x	x	x	
Serum renal chemistry, Group 2*	x	x									x	
Liver chemistry	x	x			x		x		x		x	
Hematology		x			x		x		x		x	
Urinalysis, Group 1 (see * for Group 2)	x	x	x	x	x	x	x	x	x	x	x	
Complete physical examination, Groups 1 and 2	x	x		x	x	x	x	x	x	x	x	
Changes in medical status or symptoms, Group 1 (see ł for Group 2)		x	x									

Study Procedures	Screening	Baseline	Study Week									30d Follow-Up
			4	12	24	36	48	60	72	84	96	
Drug dispensed (as required) and accountability/Concomitant medications		x	x	x	x	x	x	x	x	x	x	
Assess for AE, including renal and bone events (see ł for Group 2)		x	x	x	x	x	x	x	x	x	x	x
Pregnancy test	x	x		x	x	x	x	x	x	x	x	

Appendix 2. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18Junel2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days** **Infant, 2 – ≤ 7 Days** **Infant, 1 Day**	1000 to 1300/mm^3 1.00 to 1.30 GI/L 1250 to 1500/mm^3 1.25 to 1.50 GI/L 4000 to 5000/mm^3 4.00 to 5.00 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1000 to < 1250/mm^3 1.00 to < 1.25 GI/L 3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L 750 to < 1000/mm^3 0.75 to < 1.00 GI/L 1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 500/mm^3 < 0.50 GI/L < 750/mm^3 < 0.75 GI/L < 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:
Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure – Pediatric < 18 Years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 3. Table of Contents for Statistical Tables, Figures and Listings for the Final Analyses

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3	Demographics and Baseline Characteristics		SAS
4	Baseline Disease Characteristics		SAS
5	Concomitant Medications		SAS
6	Exposure to TDF		SAS
7	Adherence to TDF		
8.1	Number and Percentage of Subjects with HBV DNA < 400 copies/mL	by Week through Week 96 (M = E)	FAS
8.1.1	Number and Percentage of Subjects with HBV DNA < 400 copies/mL among Subjects with Normal ALT at Baseline	by Week through Week 96 (M = E)	FAS
8.1.2	Number and Percentage of Subjects with HBV DNA < 400 copies/mL among Subjects with Abnormal ALT at Baseline	by Week through Week 96 (M = E)	FAS
9	Log10 (HBV DNA) copies/mL and Change from Baseline	by Week through Week 96	FAS
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14	Number and Percentage of Subjects with HBeAg Loss/Seroconversion	by Week through Week 96 (M = E)	FAS who were HBeAg Positive at Baseline
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16	Number and Percentage of Subjects with Normalized ALT	by Week through Week 96 (M = E)	FAS with Abnormal ALT at Baseline

Table Number	Title	Title	Analysis Set
17	Number and Percentage of Subjects with HBV DNA < 400 copies/mL and Normalized ALT	by Week through Week 96 (M = E)	FAS with Abnormal ALT at Baseline
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19.1	Treatment-Emergent Adverse Events Overall Summary	Bone or Renal	SAS
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19.9	Treatment-Emergent Serious Adverse Events		SAS
19.10	Treatment-Emergent Serious Adverse Events Related to TDF		SAS
20	Treatment-Emergent Adverse Events Occurring with >= 5% Incidence in Any Monitoring Group		SAS

Table Number	Title	Title	Analysis Set
21.1	Calcium (mg/dL) and Change from Baseline		SAS
21.2	Phosphorus (mg/dL) and Change from Baseline		SAS
21.3.1	Creatinine (mg/dL) and Change from Baseline		SAS
21.3.2	Creatinine Clearance (mL/min/1.73m2) and Change from Baseline	Based on Schwartz	SAS
21.3.3	Creatinine Clearance (mL/min) and Change from Baseline	Based on Cockcroft-Gault	SAS
22.1	N-telopeptides (nmol BCE/L) and Change from Baseline		SAS
22.2	C-telopeptides (ng/mL) and Change from Baseline		SAS
22.3	Serum Osteocalcin (ng/mL) and Change from Baseline		SAS
22.4	Bone-Specific Alkaline Phosphatase (µg/L) and Change from Baseline		SAS
22.5	Serum PTH (pg/mL) and Change from Baseline		SAS
22.6	Vitamin D Level (25-hydroxy) (ng/mL) and Change from Baseline		SAS
23.1	Treatment-Emergent	Laboratory Abnormalities by Grade	SAS
23.2	Treatment-Emergent	Laboratory Abnormalities	SAS
23.3	Treatment-Emergent	Grade 3 or Grade 4 Laboratory Abnormalities	SAS
23.4	Treatment-Emergent	Marked Laboratory Abnormalities	SAS
24	Hepatic and Renal Related Abnormalities	Treatment-Emergent	SAS
25	On-Treatment ALT Flare and post treatment Exacerbation of Hepatitis		SAS
26.1	Cumulative Incidence of At Least a 4% Decrease from Baseline in Spine Bone Mineral Density (g/cm2) by Week		SAS
26.2	Percent Change from Baseline in Spine Bone Mineral Density (g/cm2) by Week	Categorical Summaries	SAS
26.3	Z-Scores for Spine Bone Mineral Density (g/cm2) and Change from Baseline by Week	Categorical Summaries	SAS

Table Number	Title	Title	Analysis Set
27.1	Cumulative Incidence of At Least a 4% Decrease from Baseline in Whole Body Bone Mineral Density (g/cm2) by Week		SAS
27.2	Percent Change from Baseline in Whole Body Bone Mineral Density (g/cm2) by Week	Categorical Summaries	SAS
27.3	Z-Scores for Whole Body Bone Mineral Density (g/cm2) and Change from Baseline by Week	Categorical Summaries	SAS

Listing Number	Title	Title	Analysis Set
1	Inclusion/Exclusion Criteria and Eligibility for Study		RAS
2	Randomization		RAS
3	Subjects Who Were Included/Excluded from Each Analysis Set		RAS
4	Demographics and Baseline Characteristics		SAS
5	Baseline Disease Characteristics		SAS
6	History of Hepatitis B Infection		SAS
7	Medical History		SAS
8	Prior Hepatitis B Medications		SAS
9	Concomitant Medications		SAS
10	Vitamin Supplements		SAS
11	Study Completion		SAS
12	TDF Administration		SAS
13	TDF Accountability		SAS
14.1	Height and Height Z-Scores		SAS
14.2	Weight and Weight Z-Scores		SAS

Listing Number	Title	Title	Analysis Set
14.3	BMI and BMI Z-Scores		SAS
15.1	Bone or Renal Adverse Events		SAS
15.2	Serious Adverse Events		SAS
15.3	Grade 3 or 4 Bone or Renal Adverse Events		SAS
15.4.1	Adverse Events Leading to Permanent TDF Discontinuation		SAS
15.4.2	Adverse Events Leading to Change in Dose or Temporary Interruption of TDF		SAS
15.5	Death Reports		SAS
16	Subjects with HBV DNA Value Above 400 copies/mL at the Final Visit		SAS
17.1.1	Laboratory Results Related to Renal Abnormalities - Part I		SAS
17.1.2	Laboratory Results Related to Renal Abnormalities - Part II		SAS
17.2.1	Grade 3 or Grade 4 Laboratory Abnormalities		SAS
17.2.2	Marked Laboratory Abnormalities		SAS
18.1	Pregnancy Tests		SAS
18.2	Pregnancy Reports		SAS
19	Comments		SAS