CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) and/or Other Oral Antiviral Treatment (OAV) in Virologically Suppressed Chronic Hepatitis B Subjects with Renal and/or Hepatic Impairment	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	115561	
EudraCT Number:	2016-004625-16	
Indication:	Chronic Hepatitis B	
Protocol ID:	GS-US-320-4035	
Gilead Sciences Study Director:	Name: Telephone: Fax: Mobile: Email:	PPD PPD PPD PPD PPD
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Protocol Version/Date:	Original: Amendment 1:	07 March 2017 23 May 2017

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) and/or Other Oral Antiviral Treatment (OAV) in Virologically Suppressed Chronic Hepatitis B Subjects with Renal and/or Hepatic Impairment
IND Number:	115561
EudraCT Number:	2016-004625-16
Study Centers Planned:	Approximately 60 centers in North America, Europe, and Asia Pacific regions
Objectives:	The primary objectives of this switch study are as follows: • To evaluate the safety and tolerability of TAF 25 mg QD at Week 24 • To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Week 24 The secondary objectives of this switch study are as follows: • To evaluate the safety and tolerability of TAF 25 mg QD at Weeks 48 and 96 • To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Weeks 48 and 96 • To evaluate biochemical (ALT normal and ALT normalization) and serological (loss of HBeAg with seroconversion to anti-HBe in HBeAg-positive subjects and loss of HBsAg with seroconversion to anti-HBs) responses at Weeks 24, 48, and 96 • To evaluate the effect of TAF 25 mg QD on renal parameters at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment and hepatically impaired subjects • To evaluate the safety of TAF 25 mg QD as determined by percentage change from Baseline in hip and spine bone mineral density (BMD) at Weeks 24, 48, and 96

- To evaluate the effect of TAF 25 mg QD on fibrosis as assessed by Fibrotest® at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on changes in Child-Pugh-Turcotte (CPT) and Model for End-stage Liver Disease (MELD) scores at Weeks 24, 48, and 96 in hepatically impaired subjects

The exploratory objectives of this switch study are as follows:

Study Design:

This is an open label, multi-center study to evaluate the safety and efficacy of switching to TAF 25 mg QD from TDF and/or other OAV in virologically suppressed subjects who have chronic hepatitis B (CHB) with renal and/or hepatic impairment.

Approximately 120 subjects will be enrolled into the 2 Parts of the study.

Part A (Renally Impaired Subjects):

Approximately 90 subjects will be enrolled into 2 cohorts and stratified by the level of renal impairment. Approximately 50% (target n = 42 to 46) of subjects enrolled into Part A should be virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF or a TDF-containing anti-HBV regimen for CHB at time of Screening.

Cohort 1: Moderate or Severe renal impairment

- Moderate renal impairment: (estimated glomerular filtration rate by the Cockcroft-Gault formula {Cockcroft 1976} 30 mL/min ≤ [$eGFR_{CG}$] ≤ 59 mL/min)
- Severe renal impairment: (15 mL/min ≤ $eGFR_{CG}$ < 30 mL/min)

  $eGFR_{CG}$ is calculated by:

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

  (Note: multiply estimated rate by 0.85 for women)

Cohort 2: End-stage renal disease (ESRD)

- Estimated glomerular filtration rate (eGFR) < 15 mL/min and maintained on hemodialysis (HD) at time of Screening

Approximately 20% (target n = 16 to 18) of subjects enrolled into Part A will be enrolled into Cohort 2.

Part B (Hepatically Impaired Subjects):

Approximately 30 subjects, all of whom are virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF, or a TDF-containing anti-HBV regimen, or other OAV(s) for CHB at time of Screening, will be enrolled with:

- Moderate hepatic impairment (CPT Class B [Appendix 7]; Score of 7-9 inclusive) OR
- Severe hepatic impairment (CPT Class C; Score of 10-12 inclusive)

The duration of study drug treatment for all subjects is 96 weeks.

Subjects in Part A (renally impaired) with HBsAg loss with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion prior to Week 24 are not permitted to discontinue study drug prior to the Week 24 visit. Subjects with HBsAg loss with confirmed seroconversion will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule (Appendix 2) through Week 96/Early Discontinuation (ED). Discontinuation of study drug for subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or compensated cirrhosis, should be considered on a case by case basis.

Subjects with moderate or severe hepatic impairment (Part B) who experience HBsAg loss and seroconversion to anti-HBs should not discontinue study drug.

Subjects in Part A (renally impaired) who permanently discontinue study drug (either prematurely or after completing 96 weeks of treatment) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or until initiation of appropriate, alternative HBV therapy, whichever occurs first. Use of appropriate, alternative HBV therapy is strongly encouraged.

For subjects in Part B (hepatically impaired) who permanently discontinue study drug, immediate initiation of appropriate, alternative HBV therapy is strongly recommended.

	A data monitoring committee (DMC) will review the progress of the study and perform review of safety data after 30 subjects have completed 12 weeks of treatment. However, Gilead will defer to the DMC for any decision to convene earlier or more frequently. The DMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies. No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study to be in the best interests of the participants.
Number of Subjects Planned:	Approximately 120 subjects will be enrolled into the 2 Parts of the study: **Part A (renally impaired; approximately 90 subjects):** Approximately 50% (target n = 42 to 46) of subjects enrolled into Part A should be virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF or a TDF-containing anti-HBV regimen for CHB at time of Screening. Approximately 20% (target n = 16 to 18) of subjects enrolled into Part A should have ESRD and be maintained on HD at time of Screening (Cohort 2). **Part B (hepatically impaired; approximately 30 subjects):** Subjects should have moderate or severe hepatic impairment and should be virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF, or a TDF-containing anti-HBV regimen, or other OAV(s) for CHB at time of Screening.
Target Population:	Adult subjects with CHB who are virologically suppressed (HBV DNA < LLOQ) for ≥ 6 months on TDF and/or other OAV treatment(s) and have renal impairment (Part A), and those who are virologically suppressed (HBV DNA < LLOQ) for ≥ 6 months on TDF, or a TDF-containing anti-HBV regimen, or other OAV(s) for CHB with hepatic impairment (Part B).
Duration of Study Drug Treatment:	96 weeks

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

Subjects must meet **all** of the following **inclusion criteria** to be eligible to participate in the study:

All Subjects (Parts A and B):

1) Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures
2) Adult male or non-pregnant female subjects, ≥ 18 years of age based on the date of the Screening visit. A negative serum pregnancy test at Screening is required for female subjects of childbearing potential (as defined in Appendix 5).
3) Documented evidence of chronic HBV infection (e.g. HBsAg positive for ≥ 6 months)
4) Normal ECG (or if abnormal, determined by the Investigator not to be clinically significant)
5) ALT ≤ 10 × upper limit of normal (ULN) at Screening by central laboratory
6) Must be willing and able to comply with all study requirements

Part A Only (renal impairment):

1) Maintained on TDF and/or other OAV treatment(s) for CHB for at least 48 weeks and with viral suppression (HBV DNA < LLOQ) for ≥ 6 months prior to Screening
   - All subjects must have HBV DNA < 20 IU/mL at Screening by central laboratory
   - Both HBeAg positive and negative subjects are eligible to participate
2) Moderate renal impairment (30 mL/min ≤ $eGFR_{CG}$ ≤ 59 mL/min), severe renal impairment (15 mL/min ≤ $eGFR_{CG}$ < 30 mL/min) using the Cockcroft-Gault equation {Cockcroft 1976}, or ESRD (eGFR < 15 mL/min) maintained on HD
   - $eGFR_{CG}$ is calculated by:

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

     (Note: multiply estimated rate by 0.85 for women)
   - Stable renal function (for subjects with moderate or severe impairment): serum creatinine measured at least once within three months prior to Screening. The measurement difference between the value measured within three months prior to Screening versus the Screening value must be ≤ 25% of the Screening value

Part B Only (hepatic impairment):

1) Maintained on TDF and/or other OAV(s) for CHB for at least 48 weeks and with viral suppression (HBV DNA < LLOQ) for ≥ 6 months prior to Screening
   - All subjects must have HBV DNA < 20 IU/mL at Screening by central laboratory
   - Both HBeAg positive and negative subjects are eligible to participate
2) CPT score (Appendix 7) of 7-12 (inclusive) OR a past history of CPT score ≥ 7 and any CPT score ≤ 12 at Screening
3) $eGFR_{CG}$ ≥ 30 mL/min using the Cockcroft-Gault equation {Cockcroft 1976}:
   - $eGFR_{CG}$ is calculated by:

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

   (Note: multiply estimated rate by 0.85 for women)

Exclusion Criteria

Subjects who meet **any** of the following **exclusion criteria** are not eligible to participate in the study:

All Subjects (Parts A & B):

1) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study
2) Males and females of reproductive potential who are unwilling to use an "effective", protocol-specified method(s) of contraception during the study (Appendix 5).
3) Co-infection with HCV, HIV, or HDV
   - Subjects who are HCV positive, but have a documented negative HCV RNA, are eligible
4) Prior Interferon (IFN) use within 6 months of Screening
5) Evidence of hepatocellular carcinoma (i.e. evidenced by imaging within 6 months of Screening)
6) Received solid organ or bone marrow transplant
7) Significant cardiovascular, pulmonary, or neurological disease in the opinion of the investigator

8) Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are not eligible
9) Currently receiving therapy with immunomodulators (e.g. corticosteroids), nephrotoxic agents, or agents capable of modifying renal excretion
10) Known hypersensitivity to study drugs, metabolites, or formulation excipients
11) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
12) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.
13) Use of investigational agents within 3 months of Screening, unless allowed by the Sponsor
14) Use of any prohibited medication as described in Section 5.3.

Part A Only (renal impairment):

1) Current or historical evidence of clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage)
2) Abnormal hematological and biochemical parameters, including:
   - Hemoglobin < 9 g/dL
   - Absolute neutrophil count < 750/mm^3
   - Platelets ≤ 50,000/mm^3
   - AST > 10 × ULN
   - Albumin < 3.0 g/dL
   - Total bilirubin > 2.5 × ULN
   - INR > 1.5 × ULN (unless stable on anticoagulant regimen)
3) Subjects with ESRD (i.e. $eGFR_{CG}$ < 15 mL/min) not on HD, or those on other forms of renal replacement therapy (i.e. peritoneal dialysis)

Part B Only (hepatic impairment):

1) Active variceal bleeding within 6 months or prior placement of a portosystemic shunt (such as transjugular intrahepatic portosystemic shunt [TIPS])
2) History of hepatorenal syndrome, hepatopulmonary syndrome, Grade 3 or Grade 4 hepatic encephalopathy, or spontaneous bacterial peritonitis within 6 months of Screening

3) Grade 2 hepatic encephalopathy at Screening
4) MELD score ≥ 30
5) Abnormal hematological and biochemical parameters, including
   - Absolute neutrophil count < 750/mm^3
   - Platelets < 30,000/mm^3
   - Hemoglobin < 8.0 g/dL

Study Procedures/ Frequency:

- Screening Visit
- Treatment Period Visits: Baseline/Day 1, Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 96/Early Discontinuation (ED)
- Subjects in Part A (renally impaired) who permanently discontinue study drug (either prematurely or after completing 96 weeks of treatment) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or until initiation of appropriate, alternative HBV therapy, whichever occurs first. Use of appropriate, alternative HBV therapy is strongly encouraged.
- For subjects in Part B (hepatic impairment) who permanently discontinue study drug, immediate initiation of appropriate, alternative HBV therapy is strongly recommended.
- Review of concomitant medications, assessment for adverse events, and vital signs and weight measurement will be conducted at all study visits.
- Laboratory analyses (serum chemistry and liver function tests, hematology, $eGFR_{CG}$, urinalysis [for all subjects except only where available for subjects in Part A, Cohort 2 (ESRD subjects on HD)], and plasma HBV DNA level) will be conducted at all study visits.

<u>Screening visit assessments include</u>:

- Complete physical examination with height, body weight, vital signs, and medical history (including HBV disease and treatment history)
- Pregnancy testing (for females of childbearing potential)
- Plasma HBV DNA level (must be < 20 IU/mL by central laboratory at time of Screening to be eligible)
- HBV serology (qualitative HBsAg and HBeAg; HBeAb and HBsAb reflex testing will be performed as needed) and quantitative HBsAg

- HCV, HDV and HIV testing
- Baseline DXA scans of the hip and spine can be performed at any time during the Screening period, but should be conducted at least 14 days prior to the first dose of study drug to ensure an acceptable pre-dose DXA scan.
- INR and alpha fetoprotein (AFP); an AFP > 50 ng/mL at Screening must have an appropriate evaluation (e.g., CT scan if not performed within the previous 6 months) in order to rule out HCC prior to being permitted to enter the study.
- CPT (Appendix 7) and MELD Scores for Part B subjects (hepatic impairment) only
- Urine drug screen (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD])
- ECG

Baseline and On Treatment assessments include:

- Complete physical examinations with body weight and vital signs will be performed at Baseline, Weeks 24, 48, 72, and 96/ED. A symptom driven physical exam will be performed at all other visits.
- Pregnancy testing (for females of childbearing potential)
- HBV serology (qualitative HBsAg and HBeAg) and quantitative HBsAg will be performed at Baseline and Weeks 12, 24, 36, 48, 60, 72, and 96/ED. HBeAb and HBsAb reflex testing will be performed as needed.
- Fasting blood sample for metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) at Baseline and Weeks 24, 48, 72, and 96/ ED
- Fibrotest® at Baseline and at Weeks 24, 48, and 96/ED
- CPT (Appendix 7) and MELD Scores at Baseline and at Weeks 24, 48, and 96/ED for Part B subjects (hepatic impairment) only
- Fracture Risk Assessment (Baseline only)
- Vitamin D assessment at Baseline and at Weeks 24 and 48
- Fasting blood for serum bone biomarkers at Baseline, and at Weeks 4, 12, 24, 48, 72, 96/ED
- Fasting urine for renal biomarkers at Baseline, and at Weeks 4, 12, 24, 48, 72, and 96/ED for all subjects except Part A, cohort 2 (ESRD subjects on HD)

- Hip and Spine DXA Scans will be conducted at Weeks 24, 48, 72, and 96/ED. The ED visit DXA should be done if not done within the last 12 weeks of this visit.
- ECG will be performed at Weeks 48 and 96/ED
- CCI [redacted]
- Sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) for resistance surveillance may be performed at Baseline for subjects with HBV DNA ≥ 69 IU/mL and may be attempted for viremic subjects (HBV DNA ≥ 69 IU/mL) at Weeks 24, 48, and 96/ED. Phenotypic analysis will be performed for subjects that are subjected to sequence analysis. As it may not be known at the time of the visit whether a subject is viremic or if it will be their last study visit, a separate virology sample for potential resistance surveillance will be collected at each study visit.
- In the event of unconfirmed virologic rebound (HBV DNA ≥ 20 IU/mL), subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw.
  - For virologic rebound occurring within the first 12 weeks of the study, the next scheduled visit will used for follow up.
  - For virologic rebound occurring after Week 12, the subject will return for an unscheduled visit 2-3 weeks after the date of the original test that resulted with HBV DNA virologic rebound for confirmation of virologic rebound. At this follow up visit, a serum blood sample for resistance testing will be obtained. For unscheduled visits, the subject will be required to bring their supply of study drug with them and be assessed for adherence by pill count, and if necessary, the subject will be re-counseled on adherence to study medication.
- Plasma, serum, and urine will be collected at Baseline and at every on-treatment visit thereafter for storage for all subjects. Urine for storage will be collected where available for subjects in Part A, Cohort 2 (ESRD subjects on HD).

- Health Related Quality of Life (HRQoL) Surveys (SF-36, CLDQ, WPAI, and EQ-5D-3L) at Baseline, Weeks 24, 48, and 96/ED. The ED visit HRQoLs should be done if not done within the last 24 weeks of this visit.
- Health Utilization Questionnaire will be administered by site staff at Baseline and at every on-treatment visit thereafter.
- Serum Cystatin C will be assessed at Baseline for all subjects. Ongoing assessments of renal function using $eGFR_{CG}$ will be done in all subjects except Part A, Cohort 2 (ESRD subjects on HD). In addition to $eGFR_{CG}$, renal function by the $eGFR_{CKD\text{-}EPI}$ formula for Cystatin C for management of potential nephrotoxicity will be assessed per Section 7.5.6.
- **Sparse PK samples**

  — All subjects except Part A, Cohort 2 (ESRD subjects on HD):

  A single PK blood sample will be collected at Baseline and at each subsequent on treatment visit. At the Week 4, Week 8, and Week 12 visit, study drug will be administered in clinic, and the single PK blood sample will be collected between 15 minutes and 4 hours post dose.

  — Part A, Cohort 2 Subjects (ESRD subjects on HD at selected sites):

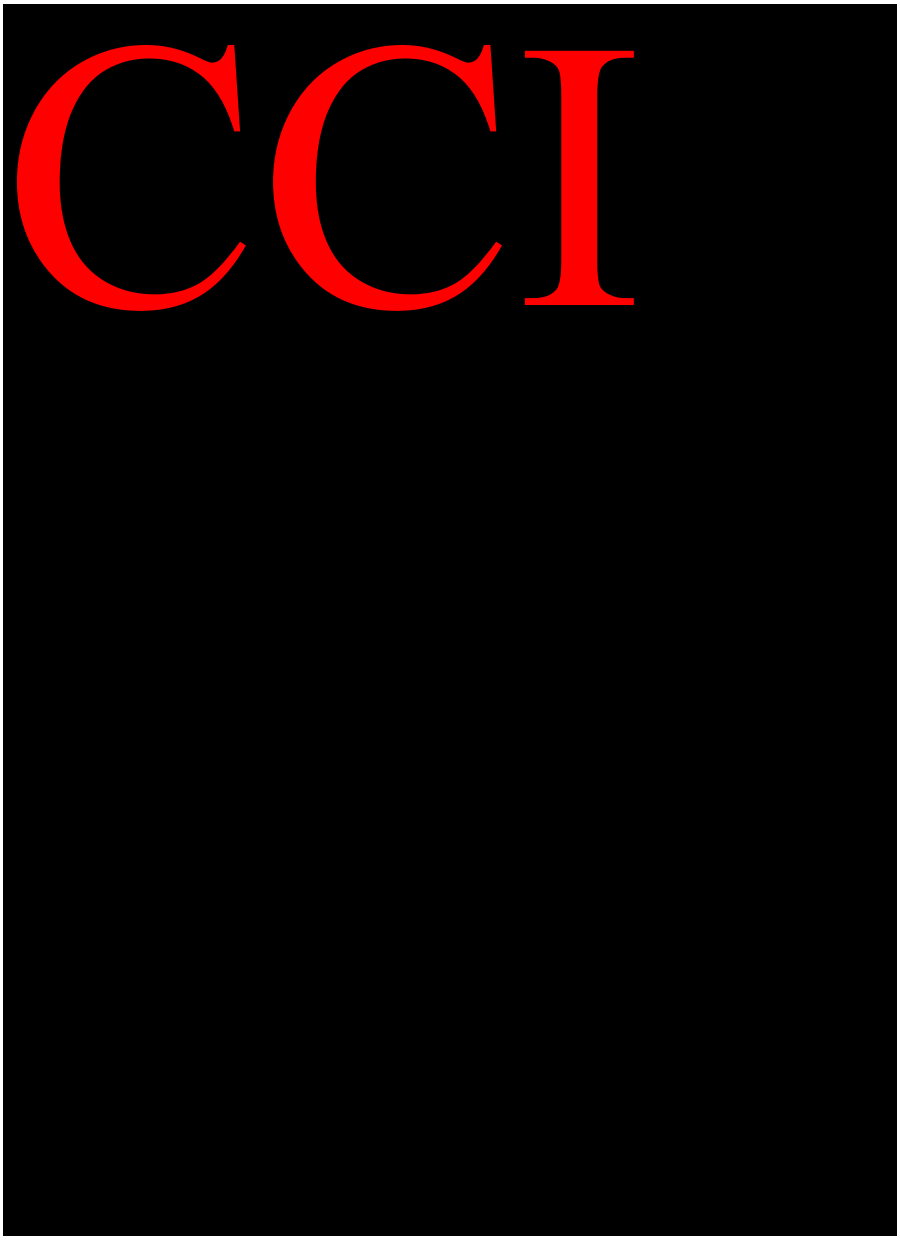
  4 samples will be collected at each of 4 hemodialysis sessions between Weeks 4 and Week 24, inclusive.

  At each session:

  - 1 sample will be collected within 10 minutes before a hemodialysis session begins
  - During the hemodialysis session, 1 sample will be collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer
  - Finally, 1 sample will be collected within 10 minutes after a hemodialysis session concludes.

  On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.

- **Optional Intensive PK Substudy (separate consent required)**



- Plasma concentrations of TAF and TFV may be determined and PK parameters (including the hemodialysis extraction ratio for Part A, Cohort 2 subjects [ESRD subjects on HD]) may be estimated as appropriate.

See Section 6 (Study Procedures) for further information.

Test Product, Dose, and Mode of Administration:	Tenofovir alafenamide (TAF) 25 mg QD, oral administration with food

Reference Therapy, Dose, and Mode of Administration:	NA

Criteria for Evaluation:

Safety:

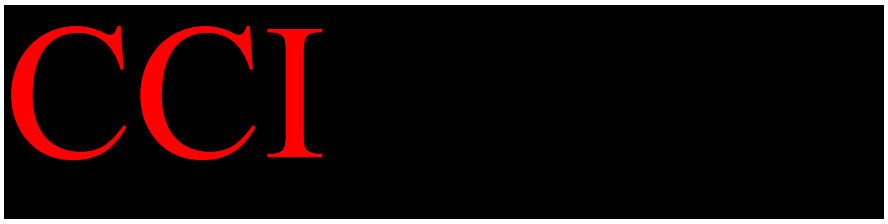
The primary safety endpoint is

- Incidence of graded adverse events and graded laboratory abnormalities at Week 24

The secondary safety endpoints are:

- Incidence of graded adverse events and graded laboratory abnormalities at Week 48 and 96
- Change from baseline in $eGFR_{CG}$ at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment and hepatically impaired subjects
- Percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24, 48, and 96

The exploratory safety endpoints are:



Efficacy:

The primary efficacy endpoint is:

- Proportion of subjects achieving virologic response (plasma HBV DNA < 20 IU/mL) at Week 24

The secondary efficacy endpoints are:

- Proportion of subjects achieving virologic response (plasma HBV DNA < 20 IU/mL) at Weeks 48 and 96
- Proportion of subjects with plasma HBV DNA < 20 IU/mL and target detected/not detected (i.e. < LLOD) at Weeks 24, 48, and 96
- Proportion of subjects with serological response (loss of HBsAg and seroconversion to anti-HBs, loss of HBeAg and seroconversion to anti-HBe in HBeAg-positive subjects) at Weeks 24, 48, and 96
- Proportion of subjects with biochemical response (normal ALT and normalized ALT) at Weeks 24, 48, and 96

	• Change in fibrosis as assessed by FibroTest® at Weeks 24, 48, and 96 • Change from baseline in CPT score (Appendix 7) and MELD score at Weeks 24, 48, and 96 in hepatically impaired subjects Other exploratory endpoints are: CCI
Pharmacokinetics:	Pharmacokinetic parameters will be listed and summarized for TAF and TFV using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum) by study Part and cohort. Plasma concentrations over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.
Statistical Methods:	The primary analysis will be performed when the last subject has completed Week 24 assessments or discontinued prematurely. The change from baseline in $eGFR_{CG}$ and $eGFR_{CKD-EPI}$ will be summarized. The change from baseline in serum creatinine will also be summarized using standard descriptive methods. The percent change from baseline in hip and spine BMD will be summarized using standard descriptive methods (ie sample size, mean, standard deviation, median, Q1, Q3, minimum, maximum). The proportion of subjects with plasma HBV DNA < 20 IU/mL will be summarized descriptively (missing = failure) (M = F). All secondary continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum). All categorical secondary endpoints will be summarized by number and percentage of subjects who meet the endpoint.
Sample Size:	No formal sample size calculation was performed. A sample size of 120 subjects is based on practical considerations and is considered sufficient to evaluate the primary objectives of the study.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	Degrees Celsius
°F	Degrees Fahrenheit
AASLD	American Association for the Study of Liver Diseases
ADV	Adefovir dipivoxil
AE	Adverse event
AFP	Alpha-fetoprotein
AhR	Aryl hydrocarbon receptor
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil counts
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Anti-HBe	Anti-Hepatitis B e-antigen
Anti-HBs	Anti-Hepatitis s-antigen
AR	Adverse reaction
ARV	Antiretroviral
AST	Aspartate aminotransferase (SGOT)
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval (tau)
BCRP	Breast Cancer Resistance Protein
BMD	Bone mineral density
BMI	Body Mass Index
B2M	Beta-2-Microglobulin
bSAP	Bone specific alkaline phosphatase
CatA	Cathepsin A
Ces1	Caboxylesterase-1
CHB	Chronic hepatitis B
CI	confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	The maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CPT	Child-Pugh-Turcotte
CRF/eCRF	case report form(s)/electronic case report form(s)
CRO	Contract (or clinical) research organization
CTX	C-type collagen sequence
CYP3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee

DNA	Deoxyribonucleic acid
DSPH	Drug Safety and Public Health
DXA	Dual energy x-ray absorptiometry
EC	Ethics committee
EC_{50}	50% Effective Concentration
EudraCT	European clinical trials database
E/C/F	Elvitegravir/cobicistat/emtricitabine
eGFR	Estimated glomerular filtration rate
$eGFR_{CG}$	Estimated glomerular filtration rate by the Cockcroft-Gault formula
EKG / ECG	Electrocardiogram
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
ESRD	End Stage Renal Disease
ETV	Entecavir
EU	European Union
EVG	Elvitegravir
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice (Guidelines)
GFR	Glomerular filtration rate
GSI	Gilead Sciences, Inc.
GGT	Gamma glutamyl transferase
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HD	Hemodialysis
HDL	High-density lipoprotein
HDV	Hepatitis D virus
HDPE	High-density polyethylene
hERG	Human ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IC_{20}	20% inhibitory concentration
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IEC	Independent ethics committee
IFN	Interferon
IMP	Investigational Medicinal Product
INR	International Normalized Ratio of Prothrombin time (INR)
IRB	Institutional review board
IVRS	Interactive voice response system
IWRS	Interactive web response system
IUD	Intrauterine device
LDL	Low-density lipoprotein
LdT	Telbivudine
LAM	Lamivudine
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantitation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MT-2	Human T-lymphotrophic virus-1 transformed cells
M = E	Missing = Excluded
M = F	Missing = Failure
NDA	New Drug Application
NOAEL	No observed adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
OAV	Oral antivirals
OL	Open-label
P1NP	Procollagen type 1 amino-terminal propeptide
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
pol	Polymerase
PXR	Pregnane X receptor
PT/INR	Prothrombin time/International normalized ratio
QD	Once daily (use only in tables)
RBP	Retinol binding protein
RPV	Rilpivirine
RT	Reverse transcriptase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sCr	Serum creatinine
SD	Standard deviation
SF-36	Short Form (36)

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STR	Single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
Scys	Serum cystatin C
TAF	Tenofovir Alafenamide, GS-7340
TAF Fumarate	Tenofovir Alafenamide Fumarate, GS-7340-03
TBV	Telbivudine
TDF	Tenofovir Disoproxil Fumarate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
TIPS	Transjugular Intrahepatic Portosystemic Shunt
T_{max}	The time (observed time point) of C_{max}
$t_{½}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_3	Triiodothyronine
UACR	Urine albumin-to-creatinine ratio
UGT1A1	Uridine glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of the normal range
UPCR	Urine protein-to-creatinine ratio
US	United States
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure {Lok 2009}. Following acute HBV infection, 5% to 10% of adults and up to 90% of children fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus {Zuckerman 1996}. Individuals who develop CHB are at substantial risk of cirrhosis, hepatic decompensation, and HCC, which will afflict 15% to 40% of subjects with CHB in the absence of effective treatment {World Health Organization (WHO) 2015a, Wright 2006}. Liver cancer is the third leading cause of cancer deaths globally, with the highest burden of disease found in regions where HBV is endemic {Global Burden of Disease Cancer Collaboration 2015}. Recent reports estimated that 250 to 350 million individuals were living with HBV (i.e., are hepatitis B surface antigen [HBsAg] positive) in 2010, representing a worldwide prevalence of 3.6%, with considerable geographic variability {Schweitzer 2015, World Health Organization (WHO) 2015b}. For example, HBV prevalence rates of 0.01%, 0.76%, 4.0%, 5.5%, and 22.4% have been reported for the United Kingdom, Canada, Turkey, China, and South Sudan, respectively. In 2013, an estimated 686,000 deaths were due to HBV infection, placing it among the top 20 causes of mortality worldwide {G. B. D. Mortality Causes of Death Collaborators 2015, Ott 2012}.

Worldwide universal vaccination remains the goal for eliminating HBV infection and its complications, yet despite the availability of HBV vaccine programs in many countries, new HBV infections are still common even in areas of low prevalence. The World Health Organization estimates that each year there are over 4 million acute clinical cases of HBV infection globally {World Health Organization (WHO) 2015b}. In the United States (US), approximately 20,000 people become acutely infected each year according to an estimate from the Centers for Disease Control and Prevention {Centers for Disease Control (CDC) 2013}.

The natural history of chronic hepatitis B virus infection and disease is complex and highly variable. Following acute hepatitis B infection, up to 90% of newborns who are vertically infected, and 25-50% of children who acquire HBV within the first 6 years of life, will become chronic carriers of the virus when the immune system is thought to be immature, compared to immunocompetent individuals who become infected during adulthood (< 1%) {Fattovich 2008, Sarin 2015}. CHB has traditionally been characterized by four distinct phases of variable duration that reflect the dynamics of viral replication and the evolving host immune response {Fattovich 2008, Sokal 2013}. In the first, or the immune tolerant phase, individuals have high plasma levels of HBV DNA, detectable hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), with normal or slightly elevated serum alanine transaminase (ALT) levels reflective of minimal inflammation and fibrosis. This phase typically extends into late childhood or adolescence, and is followed by an HBeAg-positive, immune-active phase wherein ALT levels are persistently elevated along with fluctuating levels of HBV DNA, reflective of moderate to severe inflammation or fibrosis. This phase may be followed by loss of HBeAg with seroconversion to anti-HBe. In the inactive CHB phase, subjects have undetectable or low levels

of HBV DNA (< 2000 IU/mL), the presence of anti-HBe antibody, and normal or minimal elevation in serum ALT, which reflects minimal inflammation but with variable fibrosis. This third phase can evolve in a subgroup of individuals to an HBeAg-negative, immune reactivation phase, in which ALT levels and HBV DNA levels are increased. Subjects develop HBeAg-negative CHB as a result of variants that arise in the precore or core promoter region of the virus {Sarin 2015}. The goal of anti-HBV therapy is to improve long-term survival and quality of life by reducing disease progression to cirrhosis, decompensated liver disease, and HCC {Sarin 2015, Terrault 2015}. As seroclearance of HBsAg is a rare spontaneous occurrence in patients with CHB, durable anti-HBe seroconversion in HBeAg-positive subjects is sometimes considered a reasonable endpoint, associated with improved prognosis, including a reduced risk of HCC. However, in many subjects who discontinue treatment following anti-HBe seroconversion, disease relapse with increased levels of viremia can occur {Sarin 2015}. Successful reduction of viremia to levels below assay detection leads to reduced inflammation and slowing or reversal of fibrosis, and in some patients with decompensated liver disease progression to liver failure and the need for liver transplantation is reduced {Chang 2010, Marcellin 2013}.

Currently, there are 2 approved options for treatment of CHB: injectable interferons and oral antiviral (OAV) agents. Of these, treatment with OAV agents has been more successful in achieving and maintaining a high degree of viral suppression in subjects with CHB. The development of nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) was a major breakthrough for the treatment of CHB, providing effective suppression of viral replication and reducing the risk of long-term complications {Marcellin 2013, World Health Organization (WHO) 2015a}. However, several N[t]RTIs possess a low barrier for viral resistance development, including lamivudine (LAM), telbivudine (TBV), and adefovir dipivoxil (ADV) {European Association for the Study of the Liver (EASL) 2017, Liaw 2012}. Additionally, while development of resistance to entecavir (ETV) is low in treatment-naïve subjects, the cumulative probability of ETV resistance increases substantially with long-term use in subjects, particularly in subjects who are refractory to lamivudine, and those with lamivudine resistance (up to 57% through 6 years of treatment) {Tenney 2009}. In contrast, resistance to tenofovir disoproxil fumarate (TDF; Viread®) has not been documented through 8 years of use {Kitrinos 2014, Liu 2016}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits reverse transcription in HIV-1 and HBV. TDF, an oral prodrug of TFV, was first approved for the treatment of HIV infection in 2001 to be given in combination with other antiretroviral (ARV) agents and was approved for treatment of CHB as monotherapy in 2008. TDF is currently approved in over 165 countries, including the US, Canada, Europe, Japan, Taiwan, South Korea, and China, with more than 3,393,649 patient-years of use worldwide for both HIV and HBV infections since first marketing approval. TDF is a first-line treatment for CHB in all major treatment guidelines {European Association for the Study of the Liver (EASL) 2017, Sarin 2015, Terrault 2015}. Although highly effective, use of TDF is associated with nephrotoxicity and bone-related toxicity in some subjects.

Tenofovir alafenamide (TAF) is a phosphonamide prodrug of TFV that is more stable in plasma than TDF, and provides higher intracellular levels of the active phosphorylated metabolite TFV-DP to target cells (eg, HBV-infected hepatocytes and HIV-infected lymphoid cells) with approximately 90% lower circulating levels of TFV relative to TDF at therapeutically active doses

{Agarwal 2015, Babusis 2013, Murakami 2015, Ruane 2013}. The distinct metabolism of TAF offers the potential for an improved safety profile when compared with TDF. In support of this concept are recent results from a large dataset of 1733 HIV-infected, treatment naive subjects randomized to receive treatment with the fixed-dose combination [FDC] of elvitegravir (E), cobicistat (C), emtricitabine (F), TAF [E/C/F/TAF; Genvoya®] or E/C/F/TDF [STB; Stribild®]). Renal and bone parameters were significantly less affected in subjects who received E/C/F/TAF compared with E/C/F/TDF {Sax 2015, Wohl 2016}. Furthermore, in a large open-label Phase 3 study, virally suppressed HIV-1-infected patients were switched from TDF-based regimens to a TAF-based regimen (E/C/F/TAF) with data supporting the efficacy and safety of switching regimens {Gallant 2016, Mills 2016, Pozniak 2016}. In studies of suppressed HIV-infected patients taking TDF-containing antiretroviral regimens, including those with mild or moderate renal impairment, switching to at TAF-based regimen was associated with improved bone and renal parameters while viral suppression was well maintained. In adult subjects with CHB, a global Phase 3 program for TAF consisting of 2 prospective, randomized, active-controlled studies with 1 each in HBeAg-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects is currently ongoing as described below. Efficacy and safety results at Week 48 from Studies GS-US-320-0108 and GS-US-320-0110 are summarized below in Section 1.2.3. Based on Week 48 results, TAF (Vemlidy®) was approved by the US FDA on 10 November 2016 for the treatment of CHB infection in adults with compensated liver disease {VEMLIDY® 2016}, in Japan on 19 December 2016 for the suppression of viral replication in CHB patients with evidence of HBV replication and abnormal liver function, in the European Union (EU) on 09 January 2017 for the treatment of CHB in adults and adolescents (aged 12 years and older with body weight at least 35 kg) {Vemlidy 2017}, in Australia on 21 February 2017 for the treatment of CHB in adults, and in Canada on 17 May 2017 for the treatment of CHB in adults with compensated liver disease. Marketing Applications for TAF 25 mg tablets for the treatment of CHB have been filed in a number of global territories.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy] methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1) is a novel oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase (RT) and HBV reverse transcriptase (HBV RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three forms of the drug substance have been used in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03 as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, which is being used in the Phase 3 studies GS-US-320-0108 and GS-US-320-0110, is considered comparable based on physical/chemical properties to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 1b study GS-US-320-0101. GS-7340-03 and GS-7340-02 exist as the free base, TAF, in blood and biological fluids.

For further information on TAF, please refer to the current Investigator's Brochure.

1.2.2. Preclinical Pharmacology and Toxicology

Virology

Following its release from the prodrug TAF, TFV is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HBV polymerase/reverse transcriptase (pol/RT) and HIV-1 RT that terminates the elongation of the viral DNA chain during the process of HBV and retroviral replication.

Compared to TDF, TAF is relatively stable in plasma, but rapidly converts to TFV inside cells. The cellular enzymes responsible for conversion of TAF to TFV are cathepsin A (CatA), which is broadly expressed in cells, and carboxylesterase 1 (CES1), which is highly expressed in liver. In HBV target cells, primary human hepatocytes, TAF is primarily hydrolyzed by CES1 with CatA making a minor contribution {Murakami 2015}. In HIV-1 target cells, primary human lymphoid cells, CatA is the major enzyme hydrolyzing TAF to TFV. In vitro studies have shown no significant variation for conversion to TFV and antiviral activity of TAF within PBMCs and macrophages from multiple donors. The covalent anti-hepatitis C virus (HCV) protease inhibitors (PIs) telaprevir and boceprevir were identified as the only potent inhibitors of CatA mediated hydrolysis of TAF in a biochemical assay (PC-120-2001).

TAF is a potent inhibitor of HBV replication, exhibiting in vitro activity comparable to that of TDF with an effective concentration (EC_{50}) value of 18 nM. Additionally, TAF is similarly active in vitro against wild-type genotype A-H HBV clinical isolates (PC-320-2003). TAF also exhibits potent anti-HIV activity in lymphoid T-cells, primary human PBMCs, and macrophages with EC_{50} values ranging from 3 to 14 nM. The in vitro activity of TAF against HIV-1 is 100- to 600-fold greater than TFV and 4- to 6-fold greater than TDF {Robbins 1998}. In MT-2 cells, TAF shows low cytotoxicity with a selectivity index of > 10,000. Based on data generated with the parent nucleotide TFV, TAF is active against a wide range of HIV-1 subtypes and also against HIV-2.

For further information on the virology of TAF, refer to the current Investigator's Brochure for TAF.

Safety Pharmacology

The IC_{20} and the IC_{50} for the inhibitory effect of TAF fumarate on human ether-a-go-go-related gene (hERG) potassium current was estimated to be greater than 30 µM (PC-120-2005). TAF in the monofumarate form has been evaluated to determine potential functional effects on the central nervous system (R990188), renal system (R990186), cardiovascular (D2000006), and gastrointestinal systems (R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF at 1000 mg/kg reduced distal transit and increased stomach weights starting 2 hours postdosing, with reversibility beginning by 6 hours after dosing. The no observed effect level (NOEL) for gastrointestinal motility was 100 mg/kg.

Nonclinical Pharmacokinetics

All nonclinical pharmacokinetic experiments were performed using TAF monofumarate (GS-7340-02), and all study data described reflect the dosage of the monofumarate. For reference, 100 mg of TAF monofumarate is equivalent to 80 mg of the GS-7340 free base (TAF).

Plasma pharmacokinetics of the intact prodrug, TAF, following oral administration of GS-7340-02 in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours.

Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), > 24 hours in dogs (fasted) and 8.1 to 2.5 hours in rhesus monkeys.

The tissue distribution and recovery of [^{14}C] radiolabeled GS-7340-02 was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes from all 4 sites, suggesting that TAF may be selectively cleaved to TFV in the cells of the lymphoreticular system. The primary route of elimination of TFV is renal excretion of unchanged drug based on intravenous studies of TFV. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hours. TFV was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of TFV in dogs and fecal elimination of TFV in rats and dogs are negligible.

TFV was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by CYP3A4 catalyzed oxidation (AD-120-2004). As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has limited potential to alter CYP enzyme activity through inhibition and does not inhibit UGT1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor (AhR) or human pregnane-X-receptor (PXR). These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

Nonclinical Toxicology

Because of lack of exposure to the prodrug TAF in mice and rats and achievable TFV exposures being less than previously tested in studies with TDF, Gilead and regulatory agencies have agreed that neither carcinogenicity studies nor a peri/postnatal study with TAF were warranted as they would not add to the overall risk evaluation or risk management of TAF.

The oral toxicity of TAF was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9 months. Based on recommendations that renal karyomegaly is not a dose-limiting effect {Foran 1997} and observations in the rat that renal karyomegaly is not sufficient to induce renal toxicity or predict oncogenicity (M990205) (M990204), its toxicological significance is questionable and, therefore, it was not considered an adverse effect in determining the NOAEL.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day; the 9-month dog study defined a No observed adverse effect level (NOAEL) of 2 mg/kg/day, and the 28-day nonhuman primate study defined a NOAEL of ≥ 30 mg/kg/day. While no NOAEL was determined in the 13-week mouse study, the relevance of the nasal findings to humans is unclear.

TAF had no discernible electrocardiograph effect at the low dose of 2 mg/kg/day. There was some evidence at 6 and 18/12 mg/kg/day for an effect to slightly prolong PR intervals. Additionally, at Week 39, TAF appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, significant decreases in serum tri-iodothyronine (T3) were noted for animals receiving 18/12 mg/kg/day when compared to controls, which may have been associated with the slight prolongation of PR intervals. After the 3-month recovery period, serum T3 values returned to levels similar to the control group animals at the end of the study.

TAF was not genotoxic in either in vitro or in vivo assays. TAF fumarate had no adverse effects on male or female fertility parameters in rats. There was no effect on fetal viability or fetal development in pregnant rats administered doses of TAF monofumarate up to 200 mg/kg/day or in pregnant rabbits administered TAF monofumarate up to 100 mg/kg/day the highest doses tested. In the rat, a minor (7.7%) decrease in mean fetal body weight compared to the control group was observed at 200 mg/kg/day, which was a maternally toxic dose. At the NOAEL for embryo-fetal development of 200 mg/kg/day in rats, AUC_{tau} values for TAF and TFV on Day 17 were 0.65 and 35.7 µg•h/kg, respectively. At the NOEL for embryo-fetal development of 100 mg/kg/day in rabbits, AUC_{tau} values for TAF and TFV on Day 20 were 10.7 and 23.5 µg•h/kg, respectively. The TFV exposures in both species were > 30-fold higher than the TFV AUC_{inf} after a 25-mg dose of TAF monofumarate in humans.

For further information on TAF, refer to the current investigator's brochure.

1.2.3. Clinical Trials of Tenofovir Alafenamide (TAF)

Overall, approximately 2403 subjects have been enrolled in the TAF clinical program, of which approximately 1856 subjects have received Vemlidy single agent (439 healthy volunteers, 1331 CHB infected subjects, and 86 HIV-1 infected subjects). The TAF clinical development program for CHB includes 2 ongoing Phase 3 studies in HBeAg-negative and HBeAg-positive subjects with CHB, a completed Phase 1b antiviral activity and safety/tolerability study in subjects with CHB, and a comprehensive Phase 1 program that also included evaluations of TAF and TFV PK in subjects with impaired renal or hepatic function (additional information is provided in the IB).

TAF clinical studies which are ongoing are listed below:

- **GS-US-320-1092**, a Phase 2/3 study to evaluate the pharmacokinetics, safety, and antiviral Efficacy of TAF in Adolescents with Chronic Hepatitis B Virus Infection (ongoing)

- **GS-US-320-3912**, a Phase 2 study to evaluate the efficacy and safety of TAF versus TDF 300 mg in subjects with CHB and Stage 2 or greater chronic kidney disease who have received a liver transplant (ongoing)

- **GS-US-320-4018**, a Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Switching from Tenofovir Disoproxil Fumarate (TDF) 300 mg QD to Tenofovir Alafenamide (TAF) 25mg QD in Subjects with Chronic Hepatitis B who are Virologically Suppressed (ongoing)

Please refer to the latest version of the investigator's brochure for information on the clinical program.

An overview of the 2 Phase 3 studies evaluating the efficacy and safety of TAF for Marketing Applications is provided in Table 1-1. The Phase 3 studies are described as follows:

- **GS-US-320-0108:** This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-negative subjects.

- **GS-US-320-0110:** This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-positive subjects.

In both of these similarly designed noninferiority studies, treatment naïve as well as treatment experienced subjects, including those with compensated cirrhosis, were randomized in a 2:1 ratio to receive either TAF 25 mg or TDF 300 mg once daily for 96 weeks. Randomization was stratified by plasma HBV DNA level (< 7, ≥ 7 to < 8, and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0108; < 8 and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0110) and OAV treatment status (treatment naive vs treatment experienced) at screening. In both studies, all subjects completing 96 weeks of double-blind therapy were eligible to continue open-label treatment with TAF 25 mg for an additional 48 weeks. Both protocols were amended in February 2016 (Amendment 3 of GS-US-320-0108 and GS-US-320-0110) in order to extend the duration of double-blind treatment to 144 weeks (3 years) and the duration open-label TAF treatment from Week 144 to Week 384 (8 year total study period).

Table 1-1. Clinical Studies to Support Efficacy for the TAF Marketing Applications

Study	Study Design	Treatment Regimen (Number of Subjects)	Primary Endpoint Analysis
GS-US-320-0108	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative subjects with CHB	TAF 25 mg once daily (N = 285) TDF 300 mg once daily (N = 140)	Week 48 efficacy, PK, and safety
GS-US-320-0110	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive subjects with CHB	TAF 25 mg once daily (N = 581) TDF 300 mg once daily (N = 292)	Week 48 efficacy, PK, and safety

Demographic and disease characteristics were generally similar between the TAF and TDF groups in both studies and are representative of patient population of HBeAg-negative subjects in Study GS-US-320-0108 and HBeAg-positive subjects in Study GS-US-320-0110. In both studies the majority of subjects were male (> 60%) and Asian (> 70%). As would be expected based on the 2 distinct study populations, subjects in Study GS-US-320-0108 were older (median age: 47 years; range: 19-80 years) than subjects in Study GS-US-320-0110 (median age: 36 years; range: 18-69 years). Differences in baseline characteristics between the 2 studies included HBV DNA levels (median levels were 5.7 and 7.9 $\log_{10}$ IU/mL for GS-US-320-0108 and GS-US-320-0110, respectively), serum ALT levels (median values were 67 and 85 U/L for GS-US-320-0108 and GS-US-320-0110, respectively), and number of years positive for HBV (6.0 and 4.0 years [median values] for GS-US-320-0108 and GS-US-320-0110, respectively). The distribution of HBV genotypes was similar between treatment groups in both studies with the most common genotypes being C (46.1%), D (24.3%), and B (20.4%).

Efficacy of TAF in Subjects with CHB

Primary Endpoint Analysis

For both studies, the primary efficacy endpoint was the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. Table 1-2 presents HBV DNA outcomes for Studies GS-US-320-0108 {Buti 2016} and GS-US-320-0110 {Chan 2016} for subjects at Week 48. In both studies, similar rates of HBV DNA suppression were achieved in the 2 treatment groups when assessed using the M = F method at Week 48 for the Full Analysis Set (FAS). The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows:

- **Study GS-US-320-0108:** TAF 94.0%, TDF 92.9%; difference in proportions (baseline stratum-adjusted): 1.8%, 95% CI: −3.6% to 7.2%
- **Study GS-US-320-0110:** TAF 63.9%, TDF 66.8%; difference in proportions (baseline stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%

In both studies, because the lower bound of the 2-sided 95% CI of the difference (TAF − TDF) in the response rate was greater than the prespecified −10% margin, the TAF group met the primary endpoint of noninferiority to the TDF group.

Table 1-2. GS-US-320-0108 and GS-US-320-0110: HBV DNA Outcome at Week 48 Using HBV DNA of < 29 IU/mL, Missing = Failure (Full Analysis Set)

	GS-US-320-0108		GS-US-320-0110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
HBV DNA < 29 IU/mL	268 (94.0%)	130 (92.9%)	371 (63.9%)	195 (66.8%)
P-value[a]	0.47		0.25	
Difference in Proportions (95% CI)[b]	1.8% (−3.6% to 7.2%)		−3.6% (−9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	7 (2.5%)	4 (2.9%)	183 (31.5%)	88 (30.1%)
No Virologic Data at Week 48	10 (3.5%)	6 (4.3%)	27 (4.6%)	9 (3.1%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	1 (0.2%)	0
Discontinued Study Drug Due to AE/Death	3 (1.1%)	1 (0.7%)	6 (1.0%)	3 (1.0%)
Discontinued Study Drug Due to Other Reasons[c]	6 (2.1%)	4 (2.9%)	19 (3.3%)	6 (2.1%)
Missing Data During Window but on Study Drug	1 (0.4%)	1 (0.7%)	1 (0.2%)	0

a P-value for the superiority test comparing the percentages of HBV DNA < 29 IU/mL was from the CMH test stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.
Source: GS-US-320-0108 Week 48 CSR, Section 15.1, Table 12; GS-US-320-0110 Week 48 CSR, Section 15.1, Table 12

Biochemical Analyses

Table 1-3 presents the proportion of subjects with ALT normalization at Week 48 for both studies (GS-US-320-0108) and (GS-US-320-0110) when determined by central laboratory criteria and by AASLD criteria (ULN range: ≤ 30 U/L for males and ≤ 19 U/L for females {Lok 2009, Terrault 2015}), respectively.

For Study GS-US-320-0108, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) using the central laboratory criteria was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 4 through 48. When assessed at Week 48, rates of ALT normalization were not significantly different between the 2 treatment groups by the M = F method for the Full Analysis Set (FAS). Using the AASLD criteria, the percentage of subjects with normalized ALT was significantly higher in the TAF group than in the TDF group at for all time points from Week 8 onward using the M = F method.

For Study GS-US-320-0110, the percentage of subjects with normalized ALT using the central laboratory criteria was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 8 through 48. When assessed at Week 48, rates of normalization were not significantly different between the 2 treatment groups by the M = F method for the FAS. Using the AASLD criteria, the percentage of subjects with normalized ALT was significantly higher in the TAF group than in the TDF group for all time points from Weeks 8 through 48 using the M = F method.

Overall, the percentage of subjects with normalized ALT at Week 48 was higher in Study GS-US-320-0108 compared with Study GS-US-320-0110 using the central laboratory criteria and similar across the 2 studies using the AASLD criteria.

Table 1-3. GS-US-320-0108 and GS-US-320-0110: Proportion of Subjects with ALT Normalization at Week 48, Missing = Failure (Full Analysis Set with Baseline ALT > ULN)

	GS-US-320-0108		GS-US-320-0110	
Normalized ALT	**TAF 25 mg**	**TDF 300 mg**	**TAF 25 mg**	**TDF 300 mg**
Central Laboratory[a]	**(N = 236)**	**(N = 121)**	**(N = 537)**	**(N = 268)**
Week 48	196/236 (83.1%)	91/121 (75.2%)	384/537 (71.5%)	179/268 (66.8%)
Proportion Difference (95% CI)	8.0% (−1.3% to 17.2%)		4.6% (−2.3% to 11.4%)	
p-value	0.076		0.18	
AASLD[b]	**(N = 276)**	**(N = 138)**	**(N = 572)**	**(N = 290)**
Week 48	137/276 (49.6%)	44/138 (31.9%)	257/572 (44.9%)	105/290 (36.2%)
Proportion Difference (95% CI)	17.9% (8.0% to 27.7%)		8.7% (1.8% to 15.6%)	
p-value	< 0.001		0.014	

a Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.
b AASLD ULN for ALT criteria are as follows: ≤ 30 U/L for males and ≤ 19 U/L for females.
P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata
Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
Source: GS-US-320-0108 Week 48 CSR, Section 15.1, Tables 23.1.1 and 23.2.1; GS-US-320-0110 Week 48 CSR, Section 15.1, Tables 23.1.1 and 23.2.1

Serological Analyses

In Study GS-US-320-0108, no subject in either treatment group experienced HBsAg loss by Week 48. In Study GS-US-320-0110, 4 subjects (0.7%) in the TAF group and 1 subject (0.3%) in the TDF group experienced HBsAg loss at Week 48. Three of the 4 subjects in the TAF group and none in the TDF group also experienced HBsAg seroconversion at Week 48.

In Study GS-US-320-0110, the proportion of subjects with HBeAg loss or seroconversion to anti-HBe at Week 48 was also evaluated; these data are presented on Table 1-4. A total of 78 (13.8%) and 34 (11.9%) subjects in the TAF and TDF groups, respectively, had HBeAg loss at Week 48. A total of 58 (10.3%) and 23 (8.1%) subjects in the TAF and TDF groups, respectively, experienced HBeAg seroconversion at Week 48.

Table 1-4. GS-US-320-0110: Proportion of Subjects with HBeAg Loss or Seroconversion at Week 48, Missing = Failure (Serologically Evaluable Full Analysis Set)

	GS-US-320-0110			
			TAF 25 mg vs TDF 300 mg	
	TAF 25 mg (N = 565)	TDF 300 mg (N = 285)	p-value	Prop Diff (95% CI)
HBeAg Loss, n (%)	78/565 (13.8%)	34/285 (11.9%)	0.47	1.8% (−3.0% to 6.5%)
HBeAg Seroconversion, n (%)	58/565 (10.3%)	23/285 (8.1%)	0.32	2.1% (−2.0% to 6.3%)

P-values were from the Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and oral antiviral treatment status. Differences in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion included subjects who were HBeAg positive and HBeAb negative/missing at baseline. HBeAg loss was defined as changes from HBeAg-positive at baseline to HBeAg-negative at a post-baseline visit with baseline anti-HBe negative/missing. HBeAg seroconversion was defined as HBeAg loss and anti-HBe change from negative/missing at baseline to positive at a post-baseline visit.
Source: GS-US-320-0110 Week 48 CSR, Section 15.1, Table 19.1

Virologic Resistance Analysis

In an integrated analysis of Studies GS-US-320-0108 and GS-US-320-0110, 24 subjects (2.8%) in the TAF group and 14 subjects (3.2%) in the TDF group qualified for population-based sequence analysis after up to 48 weeks of treatment. Among the 24 subjects in the TAF group who qualified for population-based sequence analysis, 15 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, and 5 had unique polymorphic site substitutions. Among the 14 subjects in the TDF treatment group who qualified for population-based sequence analysis, 6 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, 2 had unique polymorphic site substitutions, and 2 had a unique conserved site substitution. Overall, no HBV pol/RT amino acid substitutions associated with resistance to TFV were detected by sequencing and phenotypic analysis through 48 weeks of the study in either treatment group.

Safety of TAF in CHB Subjects

The principal sources of safety data for TAF are presented above in Table 1-1 and consist of 2 Phase 3 studies in subjects with CHB, Study GS-US-320-0108 and GS-US-320-0110. Subjects included in the Safety Analysis Set received at least 1 dose of study drug.

Overall Extent of Exposure

Of the 2387 subjects screened in Studies GS-US-320-0108 and GS-US-320-0110 combined, 1301 were randomized (TAF 867 subjects; TDF 434 subjects), and 1298 received at least 1 dose of study drugs (TAF 866 subjects; TDF 432 subjects); 3 subjects (TAF 1 subject; TDF 2 subjects) did not receive study drug due to withdrawal of consent. As of the Week 48 data cutoff date for each Phase 3 study, a total of 1208 subjects (TAF 93.1%, 806 subjects; TDF 93.1%, 402 subjects) were continuing double-blind study drugs, and 27 subjects (TAF 2.1%, 18 subjects; TDF 2.1%, 9 subjects) had entered the open-label phase as of the Week 48 data cutoff date. Of the 1298 subjects randomized and treated, 63 subjects (4.9%) discontinued blinded study drugs (TAF 4.8%, 42 subjects; TDF 4.9%, 21 subjects), and 61 subjects (TAF 40 subjects; TDF 21 subjects) discontinued from the study prior to the Week 48 data cutoff date. Similar rates of discontinuation and reasons for treatment discontinuation were observed for TAF compared with TDF. The most common reasons for premature discontinuation of blinded study treatment were withdrew consent (TAF 1.6%, 14 subjects; TDF 1.6%, 7 subjects); adverse event (AE; TAF 1.0%, 9 subjects; TDF 1.2%, 5 subjects); and lost to follow-up (TAF 0.7%, 6 subjects; TDF 0.7%, 3 subjects). The most common reasons for discontinuation from the study were: subjects withdrew consent (TAF 2.0%, 17 subjects; TDF 2.1%, 9 subjects), lost to follow-up (TAF 0.8%, 7 subjects; TDF 0.7%, 3 subjects), and AEs (TAF 0.3%, 3 subjects; TDF 0.9%, 4 subjects).

The median (first quartile [Q1], third quartile [Q3]) duration of exposures to blinded study drug in the TAF Phase 3 Safety Population were nearly identical between the 2 treatment groups (TAF 56.1 [48.1, 64.4] weeks; TDF 56.1 [48.1, 64.7] weeks. More than half of the subjects in each treatment group had received blinded study drug for ≥ 56 weeks at the time of the Week 48 data cutoff date for each Phase 3 study (TAF 60.5 %, 524 subjects; TDF 62.0 %, 268 subjects). There was no statistically significant difference between groups in the overall Kaplan-Meier estimate of time to premature discontinuation of blinded study drug.

Adverse Events for the TAF Phase 3 Safety Population

Summary of Adverse Events

Table 1-5 presents an overall summary of AEs by treatment group for the TAF Phase 3 Safety Population. Similar percentages of subjects in each treatment group had experienced at least 1 AE (TAF 70.2 %, 608 subjects; TDF 67.4%, 291 subjects) and had experienced at least 1 Grade 3 or 4 AE (TAF 4.5 %, 39 subjects; TDF 3.9 %, 17 subjects). In addition, 57 subjects (TAF 4.2%, 36 subjects; TDF 4.9 %, 21 subjects) had at least 1 SAE, with no subjects experiencing a treatment-related SAE. A similar percentage of subjects in each treatment group experienced an AE leading to discontinuation of study drugs (TAF 1.0%, 9 subjects; TDF 1.2%, 5 subjects). No deaths occurred in any subject on treatment. There were 2 deaths which occurred after treatment was discontinued and were considered non-treatment emergent (1 subject in each treatment group).

Table 1-5. GS-US-320-0108 and GS-US-320-0110: Overall Summary of Adverse Events in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Subjects Experiencing Any AE	608 (70.2%)	291 (67.4%)
Subjects Experiencing Any Grade 2, 3, or 4 AE	221 (25.5%)	120 (27.8%)
Subjects Experiencing Any Grade 3 or 4 AE	39 (4.5%)	17 (3.9%)
Subjects Experiencing Any Study Drug-Related AE	123 (14.2%)	68 (15.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Study Drug-Related AE	33 (3.8%)	21 (4.9%)
Subjects Experiencing Any Grade 3 or 4 Study Drug-Related AE	6 (0.7%)	2 (0.5%)
Subjects Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Subjects Experiencing Any Study Drug-Related SAE	0	0
Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation	9 (1.0%)	5 (1.2%)
Subjects Experiencing Any AE Leading to Dose Modification or Study Drug Interruption	17 (2.0%)	7 (1.6%)
Death[a]	0	0

a Treatment-emergent death refers to the death occurred between the first dose date and the last dose date (inclusive). Adverse events were mapped according to MedDRA Version 18.

Treatment-emergent AEs was defined as follows:

1) Any AEs with onset date of on or after the study drug start date and no later than the study drug stop date for those who discontinued study drug permanently, or
2) Any AE with an onset date on or after the study drugs start date for those who had not discontinued study drug permanently, or
3) Any AEs leading to study drug discontinuation

Source: TAF Week 48 ISS, Table 6

Common Adverse Events

Table 1-6 presents AEs reported for ≥ 5% of subjects for any treatment group by system organ class (SOC) and preferred term (PT) in the TAF Phase 3 Safety Population. The rate and types of AEs were similar in the 2 treatment groups. Overall, the 3 most frequently reported AEs by treatment group were as follows:

- **TAF group** — upper respiratory tract infection (9.9%, 86 subjects), nasopharyngitis (9.9%, 86 subjects), and headache (9.5%, 82 subjects)

- **TDF group** — headache (8.3%, 36 subjects), upper respiratory tract infection (7.4%, 32 subjects), and nasopharyngitis (7.2%, 31 subjects)

Table 1-6. GS-US-320-0108 and GS-US-320-0110: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects Experiencing Any Adverse Event	608 (70.2%)	291 (67.4%)
Gastrointestinal disorders	227 (26.2%)	108 (25.0%)
Nausea	43 (5.0%)	22 (5.1%)
General disorders and administration site conditions	125 (14.4%)	62 (14.4%)
Fatigue	49 (5.7%)	23 (5.3%)
Infections and infestations	259 (29.9%)	121 (28.0%)
Upper respiratory tract infection	86 (9.9%)	32 (7.4%)
Nasopharyngitis	86 (9.9%)	31 (7.2%)
Nervous system disorders	149 (17.2%)	60 (13.9%)
Headache	82 (9.5%)	36 (8.3%)
Respiratory, thoracic and mediastinal disorders	106 (12.2%)	44 (10.2%)
Cough	55 (6.4%)	27 (6.3%)

a Adverse events were mapped according to MedDRA Version 18.
b SOC were presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 7

Adverse Events by Severity

The majority of AEs reported in the TAF Phase 3 Safety Population were Grade 1 or 2. A similar percentage of subjects in each treatment group experienced at least 1 Grade 3 AE (TAF 4.5%, 39 subjects; TDF 3.9%, 17 subjects). No subjects in either group had a Grade 4 AE. The only Grade 3 AE that occurred in more than 2 subjects in either treatment group were increased ALT (TAF 0.6%, 5 subjects; TDF 0.7%, 3 subjects) and hepatocellular carcinoma (HCC) (TAF 0 subjects; TDF 0.7%, 3 subjects). Four Grade 3 ALT increases (TAF 3 subjects; TDF 1 subject) were assessed as related to study drug.

Serious Adverse Events

Table 1-7 presents SAEs reported for > 1 subjects for any treatment group in the TAF Phase 3 Safety Population. A similar percentage of subjects experienced SAEs in each treatment group (TAF 4.2%, 36 subjects; TDF 4.9%, 21 subjects). None of the SAEs were considered related to study drugs by the investigators. Hepatocellular carcinoma was reported for 6 subjects (TAF 0.1%, 1 of 866 subjects; TDF 1.2%, 5 of 432 subjects). Other SAEs reported in > 1 subject in either treatment group were cellulitis, hand fracture, dizziness, and calculus ureteric.

Table 1-7. GS-US-320-0108 and GS-US-320-0110: Serious Adverse Events by Treatment Regimen in > 1 Subject in the TAF Phase 3 Safety Population (Safety Analysis Set)

Preferred Term[a,b]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects (%) Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Hepatocellular carcinoma	1 (0.1%)	5 (1.2%)
Cellulitis	0	3 (0.7%)
Hand fracture	2 (0.2%)	0
Dizziness	2 (0.2%)	0
Calculus ureteric	2 (0.2%)	0

a Adverse events were mapped according to MedDRA Version 18.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 14

Summary of Bone Safety

Bone safety was assessed in the TAF Phase 3 Safety Population due to decreases in bone mineral density (BMD) and mineralization defects that have been seen in subjects treated with TDF.

Summary of Fractures

In the TAF Phase 3 Safety Population, the incidence of fracture events was uncommon (TAF 0.7%, 6 of 866 subjects; TDF 0.2%, 1 of 432 subjects; p = 0.44). Six of the 7 reported fractures were associated with trauma and 1 subject, in the TAF group, had a spinal compression fracture identified incidentally on a computed tomography (CT) scan. In the TAF group, 4 fractures were reported as SAEs (hand fracture [3 subjects] and 1 spinal compression fracture). In the TDF group, 1 fracture (lower limb fracture) was reported as an SAE. Of the 7 subjects who had fractures, 4 subjects in the TAF group (tibia fracture, spinal compression identified incidentally, hand fracture [2 subjects]) had normal hip and spine BMD T-scores at all timepoints, 2 subjects in the TAF group (hand fracture and traumatic spinal compression fracture) had hip and/or spine baseline BMD T-scores consistent with osteoporosis at baseline, 1 subject in the TDF group (lower limb fracture) had normal hip and spine BMD at baseline which worsened while on treatment. All fractures were considered unrelated to the study drugs by the investigators and, none resulted in discontinuation of study drugs.

Summary of Bone Mineral Density

Percentage change from baseline in hip BMD and spine BMD were the first and second key alpha-controlled safety endpoints, respectively, for both studies. Subjects receiving TAF experienced significantly less BMD reduction than those receiving TDF. At Week 48, the mean (SD) percentage decreases from baseline were as follows:

- **Hip:** TAF −0.163% (2.2437 %); TDF −1.860 % (2.4525 %)
- **Spine:** TAF −0.570 % (2.9147 %); TDF −2.366 % (3.2051 %)

Table 1-8 presents measure of BMD at Week 48. Percentage changes from baseline in hip and spine BMD were the first and second key alpha-controlled safety endpoints in Studies GS-US-320-0108 and GS-US-320-0110. Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the TAF group compared with the TDF group ($p < 0.001$). A lower percentage of subjects in the TAF group had a > 3% decrease in hip BMD compared with subjects in the TDF group (8.4% TAF; 26.7% TDF). Similarly, a lower percentage of subjects in the TAF group had a > 3% decrease in spine BMD compared with subjects in the TDF group (TAF 19.5%; TDF 38.1%). At Week 48, fewer subjects had ≥ 7% decrease in hip BMD (TAF 0.4%; TDF 2.0%) and ≥ 5% decrease in spine BMD (TAF 6.3%; TDF 20.4%) in the TAF group compared with the TDF group.

Table 1-8. GS-US-320-0108 and GS-US-320-0110: Measures of Bone Mineral Density at Week 48 (Hip DXA Analysis Set and Spine DXA Analysis Set)

	N	TAF 25 mg	N	TDF 300 mg
Hip DXA Analysis Set				
Mean (SD) Percent Change in Hip BMD	807	−0.163 (2.2437)	404	−1.860 (2.4525)
P-Value[a]	< 0.001			
Difference in LSM	1.697 (1.420, 1.974)			
Subjects with > 3% Decrease in Hip BMD, n (%)	807	68 (8.4%)	404	108 (26.7%)
P-Value[b]	< 0.001			
Subjects with > 3% Increase in Hip BMD, n (%)	807	55 (6.8%)	404	8 (2.0%)
P-Value[b]	< 0.001			
Subjects with no Decrease (≥ Zero %Change) in Hip BMD, n (%)	807	383 (47.5%)	404	83 (20.5%)
Spine DXA Analysis Set				
Mean (SD) Percent Change in Spine BMD	814	−0.570 (2.9147)	407	−2.366 (3.2051)
P-Value[a]	< 0.001			
Difference in LSM	1.796 (1.437, 2.155)			
Subjects with > 3% Decrease in Spine BMD, n (%)	814	159 (19.5%)	407	155 (38.1%)
P-Value[b]	< 0.001			
Subjects with > 3% Increase in Spine BMD, n (%)	814	89 (10.9%)	407	11 (2.7%)
P-Value[b]	< 0.001			
Subjects with no Decrease (≥ Zero %Change) in Spine BMD, n (%)	814	331 (40.7%)	407	89 (21.9%)

DXA = dual-energy x-ray absorptiometry; LSM = least-squares mean
a P-values, difference in least squares means, and its 95% CI were from the ANOVA model including treatment as a fixed effect.
b P-values were calculated from the Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).
Source: TAF Week 48 ISS, Tables 23.1.2, 23.2.2, 25.1, and 25.2 and Request 7633 Tables 2.1 and 2.2

Renal Safety

In the TAF Phase 3 Safety Population in Studies GS-US-320-0108 and GS-US-320-0110 (TAF 25 mg N = 866, TDF 300 mg N = 432; Total N = 1301), no cases of proximal renal tubulopathy (including Fanconi syndrome) or renal failure were reported in either treatment group. No subject in the TAF Phase 3 Safety population experienced a renal SAE or AE resulting in discontinuation of study drugs while on study.

Summary of Renal Laboratory Parameters

Change from baseline in serum creatinine was the third key alpha-controlled safety endpoint. Overall, increases from baseline in mean values for serum creatinine were smaller in the TAF group compared with the TDF group. Mean (SD) changes from baseline at Week 48 were 0.010 (0.1140) mg/dL for the TAF group and 0.024 (0.0974) mg/dL for the TDF group ($p = 0.012$). Graded serum creatinine abnormalities were reported for 6 subjects (0.7%) in the TAF group; all of which were Grade 1 or 2. Of the 6 subjects, 5 subjects had isolated serum creatinine elevations that were not associated with decreased eGFR. One subject, who had a relevant medical history of hypertension and diabetes, had multiple instances of graded creatinine elevations and eGFR ≤ 50 mL/min. No subjects in the TDF group had graded serum creatinine elevations.

In the TAF group, decreases from baseline in median $eGFR_{CG}$ values were significantly smaller compared with the TDF group. Median (Q1, Q3) changes from baseline at Week 48 were −1.2 (−8.4, 7.5) mL/min in the TAF group and −5.4 (−12.0, 3.0) mL/min in the TDF group ($p < 0.001$). The overall number of subjects who had any confirmed renal laboratory abnormality (ie, confirmed increases from baseline in creatinine of at least 0.5 mg/dL, or $eGFR_{CG}$ below 50 mL/min, or confirmed phosphorus < 2 mg/dL, was small (TAF 0.6%, 5 subjects; TDF 1.6%, 7 subjects). Most instances were isolated, transient, and resolved without treatment.

Summary of Proteinuria by Urinalysis (Dipstick) and by Quantitative Assessment

A similar percentage of subjects in each treatment group had at least 1 recorded, graded proteinuria by dipstick while on study; most of which were Grade 1. Table 1-9 presents a summary of the quantitative markers of proteinuria, urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR). There was a significant difference between the 2 treatment groups in median percentage changes from baseline in 1 of the quantitative markers of proteinuria UPCR at Week 48. The median (Q1, Q3) percentage change in UPCR was 6.0 (−31.0, 57.6) mg/g in the TAF group and 16.5 (−21.6, 72.4) mg/g in the TDF group ($p = 0.010$). Although not statistically significant, the median percentage change from baseline in UACR was lower in the TAF group compared with the TDF group. Median percentage changes from baseline in the markers of proximal tubular dysfunction, urine retinol binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin to creatinine ratio were smaller in the TAF group compared with the TDF group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48).

Table 1-9. GS-US-320-0108 and GS-US-320-0110: Renal Biomarkers to Urine Creatinine Ratios at Week 48 in the TAF Phase 3 Safety Population (Safety Analysis Set)

Parameter	Median Percentage Change (%) (Q1, Q3)		P-Value[a]
	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)	
UPCR (mg/g)	6.0 (−31.0, 57.6)	16.5 (−21.6, 72.4)	0.010
UACR (mg/g)	6.9 (−25.8, 46.7)	12.2 (−21.0, 63.5)	0.073
Urine RBP to Urine Creatinine Ratio (µg/g)	−0.3 (−23.2, 33.3)	25.1 (−7.9, 73.2)	< 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio (µg/g)	−3.5 (−34.3, 32.0)	37.9 (−4.6, 152.4)	< 0.001

UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio
% Change = Change from baseline at a postbaseline visit/baseline × 100%.
a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: TAF Week 48 ISS, Tables 34.1, 34.2, 34.3, and 34.4

Graded Laboratory Abnormalities

Most subjects participating in Studies GS-US-320-0108 and GS-US-320-0110 experienced at least 1 laboratory abnormality of Grade 1 or higher (TAF 94.8%, 814 of 859 subjects; TDF 91.1%, 390 of 428 subjects). The majority of subjects had abnormalities that were Grade 1 or 2 at worst severity (TAF 63.4%, 545 subjects; TDF 61.7%, 264 subjects). Grade 3 laboratory abnormalities occurred in 26.2% (225 subjects) in the TAF group and 22.4% (96 subjects) in the TDF group; Grade 4 laboratory abnormalities were less common, occurring in 5.1% (44 subjects) in the TAF group and 7.0% (30 subjects) in the TDF group. In total, a similar percentage of subjects in each group had at least 1 Grade 3 or 4 laboratory abnormality (TAF 31.3%, 269 subjects; TDF 29.4%, 126 subjects).

Table 1-10 presents a summary of the subject incidence of Grade 3 or 4 serum chemistry or urinalysis abnormalities reported for ≥ 1% in either treatment group for the overall TAF Phase 3 Safety Population. The only Grade 3 or 4 serum chemistry laboratory abnormality that occurred in > 5% of subjects overall in each of the treatment groups individually was ALT elevation (TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects). In the TDF group, Grade 3 or 4 elevations of AST also occurred in > 5% of subjects overall (TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects). Grade 3 urinalysis abnormalities included occult blood (TAF 7.7%, 66 subjects; TDF 7.0%, 30 subjects), urine erythrocytes (TAF 7.7%, 59 subjects; TDF 9.1%, 35 subjects), and urine glucose (TAF 4.8%, 41 subjects; TDF 1.2%, 5 subjects). The majority of subjects (88.6%; 124 of 140 subjects) who had Grade 3 urine occult blood or urine erythrocytes were women of child bearing potential (defined as age ≤ 54 years). The abnormalities were generally asymptomatic and not associated with AEs; none of the events were considered related to study drugs. Among the 41 subjects in the TAF group with Grade 3 urine glucose on treatment, 18 subjects (43.9%) had Grade 3 urine glucose at either screening or baseline, while the majority of the remaining 23 subjects had a medical history relevant for diabetes mellitus and/or had a graded elevation in blood glucose, or experienced an isolated and transient occurrence of Grade 3 urine glucose.

Table 1-10. GS-US-320-0108 and GS-US-320-0110: Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group in the Overall TAF Phase 3 Safety Population (Safety Analysis Set)

	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Maximum Postbaseline Toxicity Grade (N)	859	428
Grade 3	225 (26.2%)	96 (22.4%)
Grade 4	44 (5.1%)	30 (7.0%)
Chemistry		
Alanine Aminotransferase (N)	859	428
Grade 3	52 (6.1%)	27 (6.3%)
Grade 4	18 (2.1%)	13 (3.0%)
Amylase (N)	859	427
Grade 3	22 (2.6%)	9 (2.1%)
Aspartate Aminotransferase (N)	859	428
Grade 3	25 (2.9%)	18 (4.2%)
Grade 4	3 (0.3%)	5 (1.2%)
Creatine Kinase (N)	859	428
Grade 3	16 (1.9%)	7 (1.6%)
Grade 4	9 (1.0%)	6 (1.4%)
Fasting Glucose (Hyperglycemia) (N)	857	425
Grade 3	9 (1.1%)	0
Fasting LDL Cholesterol (N)	837	417
Grade 3	37 (4.4%)	1 (0.2%)
Nonfasting Glucose (Hyperglycemia) (N)	856	426
Grade 3	25 (2.9%)	7 (1.6%)
Urinalysis		
Occult Blood (N)	859	426
Grade 3	66 (7.7%)	30 (7.0%)
Urine Erythrocytes (N)	768	386
Grade 3	59 (7.7%)	35 (9.1%)
Urine Glucose (N)	859	426
Grade 3	41 (4.8%)	5 (1.2%)

Denominator for percentage (N) is the number of subjects in the safety analysis set with at least 1 postbaseline laboratory value for the test.
Subjects were counted once for the maximum postbaseline severity for each laboratory test. For urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is Grade 3.
For nonfasting glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting glucose test was not done at baseline.
'Hyper' means high and 'Hypo' means low.
Source: TAF Week 48 ISS, Table 20

Hepatic Laboratory Abnormalities

In Studies GS-US-320-0108 and GS-US-320-0110 the incidence of graded hepatic laboratory abnormalities through the Week 48 data cutoff date was generally lower for subjects in the TAF group compared with subjects in the TDF group, and included ALT increased

(TAF 22.8%,196 subjects; TDF 30.4%, 130 subjects), AST increased (TAF 22.2%, 191 subjects; TDF 25.2%, 108 subjects), total bilirubin increased (TAF 12.7%, 109 subjects; TDF 10.0%, 43 subjects), gamma-glutamyltransferase (GGT) increased (TAF 7.5%, 64 subjects; TDF 10.0%, 43 subjects), alkaline phosphatase increased (TAF 2.2%, 19 subjects; TDF 5.4%, 23 subjects), and albumin decreased (TAF 0.9%, 8 subjects; TDF 1.9%, 8 subjects).

Hepatic laboratory abnormalities in both treatment groups were generally Grade 1 or 2 at maximum severity; Grade 3 or 4 ALT abnormalities and Grade 3 or 4 AST abnormalities were observed in lower percentages of subjects in the TAF group compared with the TDF group (ALT: TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects; AST: TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects), while Grade 3 or 4 bilirubin elevations were observed in comparable percentages of subjects in the TAF group (0.3%, 3 subjects) compared with the TDF group (0.2%, 1 subject). Hepatic laboratory abnormalities were generally not associated with hepatic AEs.

Hepatic Flares

An ALT elevation was defined as treatment-emergent serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms. Through Week 48, ALT elevations were observed for 16 subjects (1.8%) in the TAF group and 9 subjects (2.1%) of subjects in the TDF group. Most of the events were at isolated time points within the first 8 weeks of dosing and resolved without recurrence while the subject remained on study drug. An ALT elevation that was confirmed at 2 consecutive postbaseline visits was considered an ALT flare. The incidence of these events was balanced between the treatment groups. Five subjects (0.6%) in the TAF group and 4 subjects (0.9%) in the TDF group had a treatment-emergent ALT flare. With the exception of 2 events, ALT flares occurred early in the dosing period; for 7 of the 9 subjects, the ALT flares resolved without recurrence while the subject remained on study drug.

Metabolic Laboratory Parameters

Administration of TDF has been associated with lower fasting low-density lipoprotein (LDL) and high-density lipoprotein (HDL) as compared with other antiviral agents. As plasma TFV exposures are approximately 90% lower with TAF administration than with TDF, fasting lipid concentrations remained relatively stable through Week 48 in the TAF treatment group, while TDF administration resulted in the expected lipid-lowering TFV effect, with decreases from baseline in fasting lipid parameters observed in the TDF group. Median decreases from baseline in total cholesterol, LDL, HDL, and triglycerides were greater in the TDF group than the TAF group, with TDF subjects demonstrating reductions in all parameters at Week 48. The difference between groups in median change from baseline was statistically significant a Week 48 for total cholesterol, direct LDL, HDL, and triglycerides ($p < 0.001$). Median (Q1, Q3) changes from baseline at Week 48 for fasting lipid parameters were as follows:

- **Total cholesterol:** TAF −2 (−17, 17) mg/dL; TDF −24 (−42, −6) mg/dL
- **LDL:** TAF 4 (−9, 20) mg/dL; TDF −9 (−25, 5) mg/dL

- **HDL:** TAF −3 (−10, 2) mg/dL; TDF −9 (−17, −3) mg/dL
- **Triglycerides:** TAF 6 (−13, 26) mg/dL; TDF −7 (−27, 10) mg/dL

The median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (−0.1, 0.5) in the TAF group and 0.2 (−0.2, 0.5) in the TDF group (p = 0.16 for the difference between treatment groups).

Eight subjects (0.9%) in the TAF group had Grade 3 elevated fasting cholesterol; 7 of the 8 subjects had a history of hyperlipidemia and/or elevated fasting cholesterol at baseline. There were no subjects with Grade 4 elevated fasting cholesterol in the TAF group, and none with Grade 3 or 4 elevated fasting cholesterol in the TDF group. Thirty-seven subjects (4.4%) in the TAF group and 1 subject (0.2%) in the TDF group had Grade 3 elevated fasting LDL. Overall, changes in median values of total cholesterol, LDL, HDL, and triglycerides in the TAF group were not clinically relevant, and none of the subjects with Grade 3 elevations in fasting lipids had clinical AEs associated with lipid abnormalities.

1.2.4. Clinical Trials of Tenofovir Alafenamide in Subjects with Renal Impairment

1.2.4.1. Phase 1 Study of Tenofovir Alafenamide in Subjects with Renal Impairment (GS-US-120-0108)

A Phase 1 open-label study was performed to evaluate the PK of TAF and its metabolite TFV in subjects without HIV or HBV infection and with severe renal impairment (defined as subjects with eGFR$_{CG}$ between 15 and 29 mL/min [inclusive] who were not on dialysis) and in age- and sex-matched subjects with normal renal function (eGFR$_{CG}$ ≥ 90 mL/min) following a single dose of TAF 25 mg {Custodio 2016}. Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by AUC$_{inf}$) relative to age- and sex-matched subjects with normal renal function (Table 1-11).

Table 1-11. GS-US-120-0108: Statistical Comparisons of TAF PK Parameter Estimates in Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

TAF PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test Severe Renal Impairment (N = 14)	Reference Normal Renal Function (N = 13)	
AUC$_{inf}$ (ng•h/mL)	513.2 (47.3)	267.3 (49.2)	191.89 (137.81, 267.18)
AUC$_{last}$ (ng•h/mL)	510.6 (47.4)	265.9 (49.5)	192.26 (137.81, 268.21)
C$_{max}$ (ng/mL)	363.7 (65.7)	198.8 (62.1)	179.43 (123.73, 260.20)

Source: GS-US-120-0108, Section 15.1, Tables 4.1 and 6.1

Additionally, based on population PK analyses of pooled data from Phase 3 studies in subjects with CHB receiving TAF, baseline $eGFR_{CG}$ was not a statistically significant or clinically relevant covariate influencing TAF PK which is consistent with the established PK profile of TAF from the E/C/F/TAF development program that included a dedicated study in HIV-infected subjects with mild to moderate renal impairment {Pozniak 2016}. Accordingly, as $eGFR_{CG}$ is not covariate for TAF, no clinically relevant exposure differences are anticipated in subjects with various degrees of renal impairment following administration of TAF, including in ESRD with HD.

In line with its renal route of elimination, following a single dose of TAF, subjects with severe renal impairment (Study GS-US-120-0108) had a 5.7-fold increase in systemic TFV exposure (as assessed by AUC_{inf}) relative to age- and sex-matched subjects with normal renal function (Table 1-12). The plasma TFV exposure observed in this study in subjects with severe renal impairment was below the exposure observed in historical studies after administration of TDF 300 mg in subjects with normal renal function (3300 ng•h/mL) {Gilead Sciences Inc. 2015, Gilead Sciences Ltd 2016}.

Table 1-12. GS-US-120-0108: Statistical Comparisons of TFV PK Parameter Estimates Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

TFV PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test Severe Renal Impairment (N = 14)	Reference Normal Renal Function (N = 13)	
AUC_{inf} (ng•h/mL)	2073.8 (47.1)	342.6 (27.2)	573.76 (457.21, 720.01)
AUC_{last} (ng•h/mL)	1694.9 (43.1)	298.0 (26.1)	545.91 (442.82, 672.99)
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)	279.31 (231.48, 337.02)

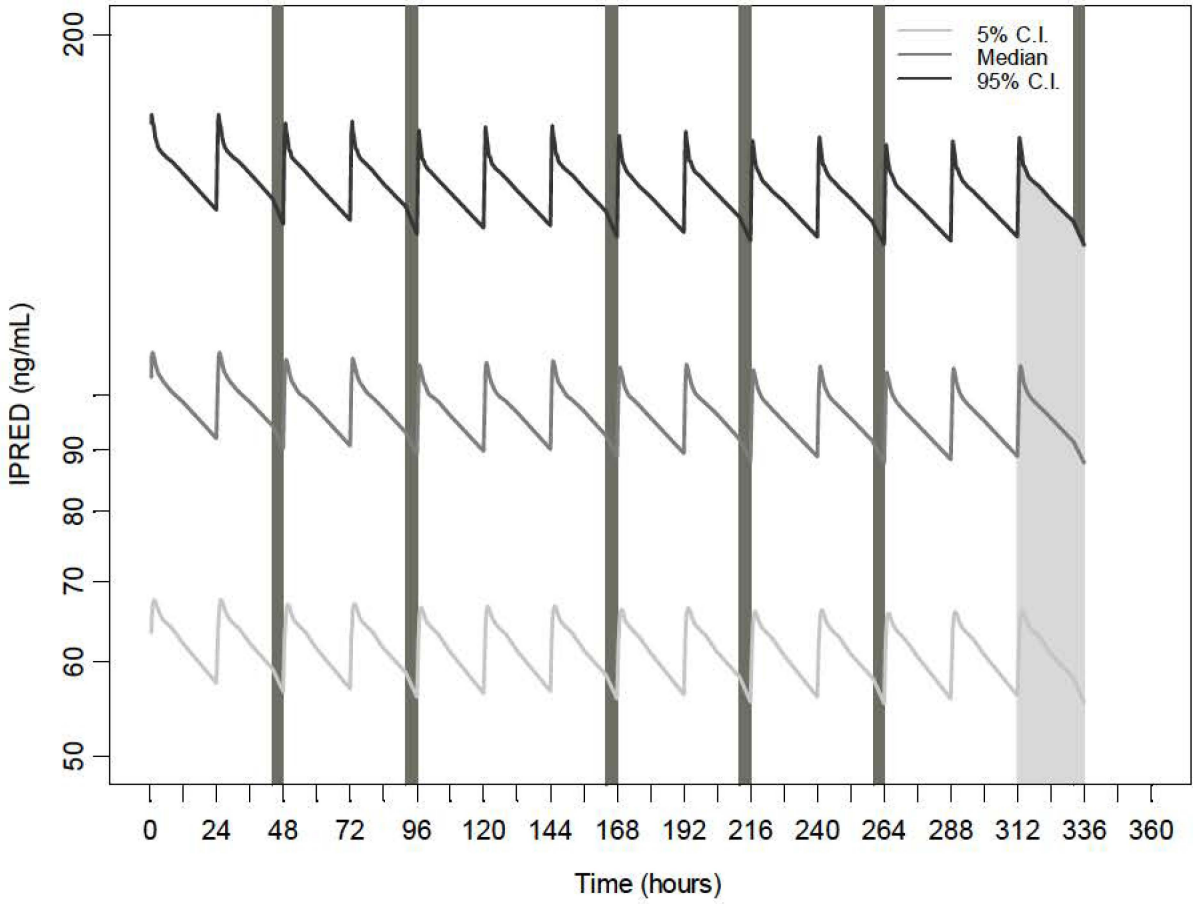
Source: GS-US-120-0108, Section 15.1, Tables 4.2 and 6.1

TAF Population Pharmacokinetics and PK Modelling of TAF and TFV in Subjects with End-Stage Renal Disease on Hemodialysis

Based on popultion PK analyses of the pooled data from Phase 3 studies in subjects with CHB receiving TAF, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses. These findings were expected with TFV being primarily renally eliminated. Although TFV exposure was higher in subjects with CHB with lower baseline $eGFR_{CG}$ relative to those with normal renal function, the TFV exposure observed in subjects with CHB with renal function $30 \leq eGFR_{CG} < 60$ mL/min receiving TAF (515.8 ng•h/mL) was below the exposure observed in historical studies after administration of TDF 300 mg in subjects with normal renal function (3300 ng•h/mL) {Gilead Sciences Inc. 2015, Gilead Sciences Ltd 2016}.

As $eGFR_{CG}$ is not covariate for TAF, no clinically relevant differences in TAF exposure are expected in subjects with ESRD on HD. However, for the renally eliminated metabolite TFV, simulation was conducted to predict TFV exposures using the population PK model for TFV following once-daily administration of TAF 25 mg in subjects with ESRD on HD, incorporating information on the HD clearance of plasma TFV from a previously conducted Gilead Study (GS-01-919) {Kearney 2006} where TDF 300 mg was administered in subjects with ESRD (Figure 1-1).

Figure 1-1. Predicted Steady-State TFV PK Profile After Administration of TAF in Subjects With CHB with ESRD on Chronic HD



Simulated TFV PK profile following TAF once daily for 2 weeks in subjects with ESRD on chronic HD 3 times per week. IPRED represents the model-predicted plasma concentration of TFV. The shaded regions in dark gray represent HD duration (4 hours) and interval. HD session(s) on the first week (0-156 hours) are represented during the time intervals of 44-48 hours and 92-96 hours; in the second week (156-324 hours) are represented during the time intervals 164-168 hours, 212-216 hours, and 260-264 hours; and in the third week (324-336 hours) is represented during the time interval 332-336 hours. The shaded region in light gray represents steady-state, maximum TFV exposure that was used in calculation of PK parameters.
Source: TAF HBV ESRD Modeling Report

In subjects with CHB with ESRD on chronic HD 3 times per week, systemic TFV exposures are expected to be higher following administration of TAF relative to administration of TAF in subjects with $eGFR_{CG} \geq 30$ mL/min, due to reduced renal function and the resulting decreased elimination of TFV. TAF administered once daily in subjects on chronic HD 3 times per week is predicted to result in a mean (%CV) TFV exposure of 2360 (26.7) ng•h/mL. Given the extensive safety data available for TDF in HIV-infected subjects and those with CHB, TFV exposures following administration of TAF in subjects with CHB with ESRD on chronic HD are expected to be in the range of those following TDF-containing regimens in patients with normal renal function and, as such, a dose modification of TAF would not be required in this population.

In line with these results, no dose adjustment of TAF is required in patients with mild, moderate or severe renal impairment {Vemlidy 2017, VEMLIDY® 2016}. In accordance with the EU Summary of Product Characteristics (SmPC), TAF may be used in patients with ESRD who are receiving hemodialysis {Vemlidy 2017}.

1.2.4.2. Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide in HIV-1 Positive Patients with Mild to Moderate Renal Impairment (GS-US-292-0112)

GS-US-292-0112, is a single-arm, Phase 3 open-label safety study of E/C/F/TAF in virally suppressed HIV-1 positive patients with mild to moderate renal impairment (eGFR 30 - 69 mL/min), including 65% who were suppressed on antiretroviral regimens containing TDF. In this study, a total of 242 patients were treated (80 patients with eGFR < 50 mL/min and 162 patients with eGFR ≥ 50 mL/min) {Pozniak 2016}. At Week 48, patients who switched to E/C/F/TAF had no change in eGFR, and had significant improvements in measures of renal function including proteinuria, albuminuria, retinol binding protein and beta-2-microglobulin ($p < 0.001$ for all). These subjects also had improvements in measures of bone mineral density (mean % change of +1.47% and 2.29% for hip and spine BMD, respectively, $p < 0.05$). In addition, 92% of study participants maintained virologic suppression (HIV-1 RNA < 50 copies/ml) at Week 48 after switching to E/C/F/TAF.

1.2.4.3. Safety and Efficacy of TDF in CHB Patients with Decompensated Liver Disease (Study GS-US-174-0108)

The safety and efficacy of TAF have not been evaluated in CHB patients with decompensated cirrhosis (CPT Class B and C). Given that TAF demonstrated non-inferior efficacy to TDF in HBeAg-negative (GS-US-320-0108) and HBeAg-positive (GS-US-320-0110) patients with CHB, including patients with compensated cirrhosis, it is important to consider results from TDF clinical studies as background to assessing the potential efficacy and safety of TAF in patients with decompensated liver disease.

The safety and efficacy of TDF in patients with decompensated liver disease were assessed in a double-blind, randomized, active controlled Phase 2 study (GS-US-174-0108) {Liaw 2011}. One hundred twelve CHB patients with decompensated liver disease (CPT score ≥ 7 and ≤ 12) with screening HBV DNA ≥ 10^3 copies/mL and creatinine clearance ≥ 50 mL/min (by Cockcroft-Gault method) were randomized 2:2:1 to receive TDF 300 mg once daily (n = 45),

emtricitabine (FTC)/TDF 200 mg/300 mg once daily (n = 45), or entecavir (ETV) (n = 22). Patients randomized to ETV were dosed at 0.5 mg once daily or 1.0 mg once daily in those with prior LAM exposure (≥ 6 months of LAM treatment and/or history of LAM resistance mutations). Patients with inadequate early viral suppression (i.e. < 2 $\log_{10}$ decrease in HBV DNA at Week 8), those with virologic breakthrough (i.e. ≥ 1 $\log_{10}$ increase from nadir), or patients with confirmed HBV DNA ≥ 69 IU/mL (≥ 400 copies/mL) could be switched to open-label FTC/TDF treatment at the investigator's discretion; however, these patients were declared treatment failures at time of switch. Patients undergoing orthotopic liver transplantation (OLT) were allowed to continue on study but were censored in regard to secondary efficacy analyses at the time of liver transplant.

The co-primary endpoints of GS-US-174-0108 were proportion with tolerability failure (adverse event [AE] resulting in permanent study drug discontinuation), and confirmed renal event (an increase from baseline in serum creatinine [sCr] of ≥ 0.5 mg/dL or decrease in serum phosphate [PO_4] below 2.0 mg/dL). At Week 48, rates of tolerability failure were comparable across treatment groups (TDF 6.7%, FTC/TDF 4.4%, ETV 9.1%). Confirmed increases in sCr or decreases in PO_4 occurred in a similar percentage of patients in the TDF and FTC/TDF groups (8.9% and 6.7%, respectively); however, confirmed renal events occurred in a lower percentage of ETV-treated patients (4.5%). The percentages of patients with AEs and SAEs considered related to study drug, and AEs resulting in permanent study drug discontinuation, or treatment emergent deaths (2 subjects in each group), were low and similar between treatment groups.

Although the study was not sufficiently powered to assess antiviral efficacy, the proportions of patients (95% confidence interval) in GS-US-174-0108 achieving HBV DNA < 69 IU/mL (< 400 copies/mL) at Week 48 were comparable between treatment groups (TDF 70% [57%, 84%], FTC/TDF 88% [78%, 98%], ETV 73% [54%, 91%] when evaluated by non-completers or switch equals failure [NC/S=F]), as were the rates of ALT normalization (TDF 46% [27%, 65%], FTC/TDF 64% [45%. 83%], ETV 41% 18%, 65%] [NC/S=F]). No patient in any treatment group developed resistance to study drug, and similar percentages of patients in each group showed improvements in CPT and model for end-stage liver disease (MELD) scores at Week 48 {Liaw 2011}.

When patients in GS-US-174-0108 were followed longer-term, a total of 69/112 (62%) patients completed 168 weeks of double-blind therapy with 12 (6-TDF, 3-FTC/TDF, and 3-ETV) patients switching to open-label FTC/TDF (10 patients prior to Week 48), and 11 (3-TDF, 7-FTC/TDF, 1-ETV) patients receiving OLT (8 of 11patients completed the study through 168 weeks). In general, the safety and efficacy of TDF, FTC/TDF, and ETV were comparable and maintained through Week 168. No TDF resistance was documented over the entire (168 weeks) duration of treatment.

1.3. Rationale for this Study

As the population of patients with CHB ages, the prevalence of chronic kidney disease (CKD) will likely increase along with the increasing development of co-morbid conditions that require medical management {Kazancioglu 2013, Pipili 2013}. This population is also more vulnerable to bone loss as well as renal complications {Chen 2015a, Chen 2015b}. Recent evidence from

prospective cohort studies in Taiwan suggest that the risk of CKD is significantly higher in individuals with CHB compared to those without CHB {Chen 2015b}, and that CHB infection increases the risk of developing ESRD (12-year cumulative incidence 1.9% compared with 0.49% for CHB and non\-CHB cohorts, respectively) {Chen 2015c}. In another analysis from the Taiwan nationwide cohort, patients with CHB demonstrated an increased risk of osteoporosis compared with a comparison cohort without CHB; the incidence of this complication increased with advancing age (adjusted hazard ratio [aHR], 95% confidence interval, 13.3 [11.8-14.9] for age ≥ 65 years), and coexisting cirrhosis (aHR 1.62 [1.24-2.12]) {Chen 2015a}.

Further, the patient population with CHB and CKD is complex requiring special treatment strategies. Interferons are poorly tolerated in this population, and in addition, all of the oral nucleos(t)ide reverse transcriptase inhibitors (e.g. LAM, ADV, TBV, ETV, and TDF) approved for the treatment of CHB must undergo dose modification in patients with renal impairment to avoid accumulation due to predominant renal elimination pathways {Pipili 2013}. Increased monitoring is also required for certain OAVs such as ADV and TDF due to the increased risk of renal complications in patients with underlying renal compromise {Amet 2015}. While ETV has demonstrated high potency and a good safety/tolerability profile in treatment naïve patients with CHB, increased rates of resistance development have been seen in patients previously treated with LAM {Tenney 2009}, making ETV a less useful treatment option for many patients, including those with CKD. Thus, there remains a need for new options for the treatment of CHB in patients with CKD.

Given the current lack of clinical data for TAF in patients with CHB and CKD, the present study (Part A) is being undertaken to evaluate the safety and efficacy of TAF 25 mg given once daily in CHB patients with moderate or severe renal impairment, and includes a cohort of subjects with ESRD patients who are maintained on chronic HD.

Subjects with decompensated liver disease and active HBV replication are at increased risk of developing progressive liver disease and death {Fattovich 1991}. Furthermore, renal complications occur more commonly in this population, and CHB patients with cirrhosis are also more prone to bone loss and osteoporosis {Chen 2015a}. Peg-IFN is contraindicated in the setting of decompensated liver disease; OAV therapy with either TDF or ETV is recommended {European Association for the Study of the Liver (EASL) 2017, Sarin 2015, Terrault 2015}. With the advent of these potent OAVs for CHB, clinical disease progression can be slowed or reversed {Chang 2010, Marcellin 2013}, and fewer patients with established decompensated liver disease will require liver transplantation while under potent anti-HBV treatment {Zanetto 2016}. While results from Study GS-US-174-0108 suggest that TDF improves the clinical course of patients with decompensated liver disease and is generally safe and well tolerated, confirmed renal abnormalities were observed in a higher percentage of TDF-treated patients compared to those treated with ETV {Liaw 2012}. Results from a recent retrospective analysis in India of 400 CHB patients with cirrhosis, including 210 patients with decompensated liver disease without access to liver transplantation, who were treated with TDF (55%) or ETV (45%) showed higher rates of nephrotoxicity (sCr increase ≥ 0.5 mg/dL from baseline) with TDF compared with ETV (5% vs. 1%) when followed for a median of 45 and 36 months, respectively {Goyal 2015}.

Given 90% lower TFV exposures from TAF 25 mg relative to TDF 300 mg once daily, and lack of clinically relevant alteration in the PK of TAF or TFV in moderate or severe hepatic impairment, TAF 25 mg offers the potential for an improved safety profile in CHB patients with hepatic impairment. This study (Part B) will include a cohort of subjects with CPT Class B or C (CPT score 7 to 12 [inclusive]) cirrhosis to assess the safety and efficacy of TAF in this important patient population.

1.4. Risk/Benefit Assessment for the Study

In the setting of renal impairment, TAF represents an important new option given its potent efficacy and absence of resistance (through 48 weeks of treatment), and the lack of need for dose adjustment. This is supported by pharmacokinetic data, safety data in HIV-1 patients and underlying renal impairment treated with E/C/F/TAF once daily over 48 weeks, and by PK simulation of subjects with ESRD on HD. Further, in Studies GS-US-320-0108 and GS-US-320-0110 conducted in treatment naïve and experienced patients with CHB and $eGFR_{CG} \geq 50$ mL/min, TAF has demonstrated improved renal and bone safety compared with TDF. Thus, patients with CHB, particularly those with CKD who are suppressed on oral antiviral therapy including TDF, may benefit from switching therapy to TAF in regard to maintenance of viral suppression with the potential for improved bone parameters and maintenance or improvement in renal parameters.

In CHB patients with decompensated liver disease (CPT Class B and C), TAF offers the advantages of potent antiviral therapy without resistance development with the potential for improved bone and renal safety. This is important given that fewer patients with decompensated cirrhosis experience disease progression requiring liver transplantation, and life-long therapy is required in this special population.

Potential risks of a patient's involvement in this study include switching to a new treatment regimen with the potential loss of virologic control and/or emergence of new adverse events. Other risks common to clinical trials such as this include the inconvenience of frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include frequent monitoring of viral load and other laboratory parameters as well as ongoing monitoring of adverse events. Parameters for discontinuation of study drug due to adverse events or lack of efficacy are well-defined and will be closely followed. In addition, an independent data monitoring committee will be convened early in the course of the study to evaluate safety data and determine whether the risks/benefits warrant continuation of the study.

Considering the above, the benefit-risk balance for this study is considered positive.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the safety and tolerability of TAF 25 mg QD at Week 24
- To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Week 24

The secondary objectives of this study are:

- To evaluate the safety and tolerability of TAF 25 mg QD at Weeks 48 and 96
- To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Weeks 48 and 96
- To evaluate biochemical (ALT normal and ALT normalization) and serological (loss of HBeAg with seroconversion to anti-HBe in HBeAg-positive subjects and loss of HBsAg with seroconversion to anti-HBs) responses at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on renal parameters at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment and hepatically impaired subjects
- To evaluate the safety of TAF 25 mg QD as determined by percentage change from Baseline in hip and spine bone mineral density (BMD) at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on fibrosis as assessed by Fibrotest® at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on changes in Child-Pugh-Turcotte (CPT) and Model for End-stage Liver Disease (MELD) scores at Weeks 24, 48, and 96 in hepatically impaired subjects

The exploratory objectives of this study are as follows:

3. STUDY DESIGN

3.1. Study Treatment Plan and Regimen

This is an open label, multi-center study to evaluate the safety and efficacy of switching to TAF 25 mg QD from TDF and/or other OAV in virologically suppressed subjects who have CHB with renal and/or hepatic impairment.

Approximately 120 subjects will be enrolled into the 2 Parts of the study:

Part A (Renally Impaired subjects):

Approximately 90 subjects will be enrolled into 2 cohorts and stratified by the level of renal impairment. Approximately 50% of subjects (target n = 42 to 46) enrolled into Part A should be virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF or a TDF-containing anti-HBV regimen for CHB at time of Screening.

Cohort 1: Moderate or Severe renal impairment

- Moderate renal impairment (30 mL/min ≤ $eGFR_{CG}$ ≤ 59 mL/min)
- Severe renal impairment (15 mL/min ≤ $eGFR_{CG}$ < 30 mL/min)

  $eGFR_{CG}$ is calculated by:

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

  (Note: multiply estimated rate by 0.85 for women)

Cohort 2: ESRD (eGFR < 15 mL/min) and maintained on HD

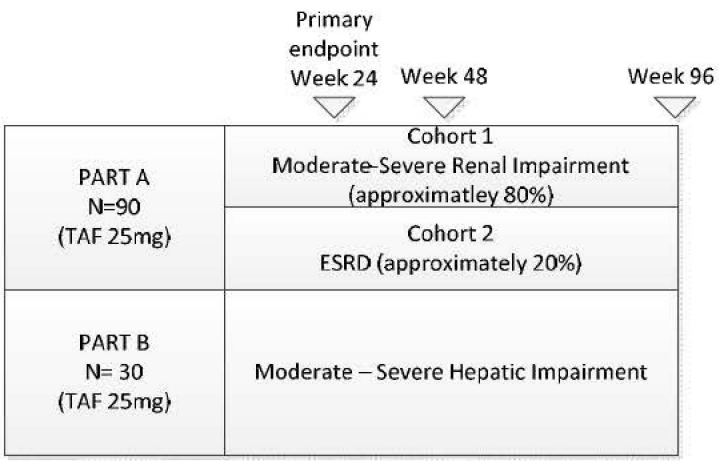
Approximately 20% of subjects (target n = 16 to 18) enrolled into Part A will be enrolled into Cohort 2.

Part B (Hepatically Impaired Subjects):

Approximately 30 subjects, all of whom are virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF, or a TDF-containing anti-HBV regimen, or other OAV(s) for CHB at time of Screening will be enrolled with:

- Moderate hepatic impairment (CPT [Appendix 7] Class B; Score of 7-9 inclusive) OR
- Severe hepatic impairment (CPT Class C; Score of 10-12 inclusive)

Figure 3-1. Study Design Schematic



The duration of study drug treatment for all subjects is 96 weeks.

Subjects in Part A (renally impaired) with HBsAg loss with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion prior to Week 24 are not permitted to discontinue study drug prior to the Week 24 visit. Subjects with HBsAg loss with confirmed seroconversion will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule (Appendix 2) through Week 96/Early Discontinuation (ED). Discontinuation of study drug for subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or compensated cirrhosis, should be considered on a case by case basis.

Subjects with moderate or severe hepatic impairment (Part B) who experience HBsAg loss and seroconversion to anti-HBs should not discontinue study drug.

Subjects in Part A (renally impaired) who permanently discontinue study drug (either prematurely or after completing 96 weeks of treatment) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or until initiation of appropriate, alternative HBV therapy, whichever occurs first. Use of appropriate, alternative HBV therapy is strongly encouraged.

For subjects in Part B (hepatic impairment) who permanently discontinue study drug, immediate initiation of appropriate, alternative HBV therapy is strongly recommended.

A data monitoring committee (DMC) will review the progress of the study and perform review of safety data after 30 subjects have completed 12 weeks of treatment. However, Gilead will defer to the DMC for any decision to convene earlier or more frequently. The DMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies. No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study to be in the best interests of the participants.

3.2. Biomarker Testing

3.2.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to evaluate the association of biomarkers with study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of chronic hepatitis B and related diseases. The specific analyses will include, but will not be limited to, the biomarkers listed below. Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

- Urine Biomarkers including, but not limited to, retinol binding protein (RBP) and beta-2 microglobulin (for all subjects in Part A except Cohort 2 (ESRD subjects on HD) and all subjects in Part B [hepatic impairment])

- Serum Bone Biomarkers including, but not limited to, C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP)

These specimens will be collected in a fasted state at Baseline and Weeks 4, 12, 24, 48, 72, and 96/ED. Samples may be stored by Gilead Sciences for a period of up to 15 years at the end of the study.

3.2.2. Biomarker Samples for Optional Future Research

CCI [redacted]

3.2.3. Biomarker Samples for Optional Pharmacogenomic Research

CCI [redacted]

3.3. End of Study

The end of the study will be the last subjects' last observation or visit.

3.4. Post Study Care

Once a subject has completed their study participation, the long-term care of the participant will return to the responsibility of their primary treating physicians.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 120 subjects will be enrolled into Part A (renal impairment) and Part B (hepatic impairment). In Part A, approximately 90 subjects will be enrolled with approximately 50% of subjects (target n = 42 to 46) virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF or a TDF-containing anti-HBV regimen for CHB at time of Screening, and with approximately 20% of subjects (target n = 16 to 18) having ESRD and maintained on HD at time of Screening. In Part B, approximately 30 subjects will be enrolled, all of whom should be virologically suppressed (HBV DNA < LLOQ) for at least 6 months on TDF, or a TDF-containing anti-HBV regimen, or other OAV(s) for CHB at time of Screening and have moderate or severe hepatic impairment.

4.2. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible to participate in this study.

All Subjects (Parts A and B):

1) Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures

2) Adult male or non-pregnant female subjects, ≥ 18 years of age based on the date of the Screening visit. A negative serum pregnancy test at Screening is required for female subjects of childbearing potential (as defined in Appendix 5)

3) Documented evidence of chronic HBV infection previously (e.g., documented HBsAg positive for ≥ 6 months)

4) Normal ECG (or if abnormal, determined by the Investigator not to be clinically significant)

5) ALT ≤ 10 × ULN at Screening by central laboratory

6) Must be willing and able to comply with all study requirements

Part A Only (renal impairment):

1) Maintained on TDF and/or other OAV treatment(s) for CHB for at least 48 weeks and with viral suppression (HBV DNA < LLOQ) for ≥ 6 months prior to Screening

   - All subjects must have HBV DNA < 20 IU/mL at Screening by central laboratory
   - Both HBeAg positive and negative subjects are eligible to participate

2) Moderate renal impairment (30 mL/min ≤ $eGFR_{CG}$ ≤ 59 mL/min), severe renal impairment (15 mL/min ≤ $eGFR_{CG}$ < 30 mL/min) using the Cockcroft-Gault equation {Cockcroft 1976}, or ESRD (eGFR < 15 mL/min) maintained on HD

   - $eGFR_{CG}$ is calculated by:

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

     (Note: multiply estimated rate by 0.85 for women)

   - Stable renal function (for subjects with moderate or severe impairment): serum creatinine measured at least once within three months prior to Screening. The measurement difference between the value measured within three months prior to Screening versus the Screening value must be ≤ 25% of the Screening value

Part B Only (hepatic impairment):

1) Maintained on TDF and/or other OAV treatment(s) for CHB for at least 48 weeks and with viral suppression (HBV DNA < LLOQ) for ≥ 6 months prior to Screening

   - All subjects must have HBV DNA < 20 IU/mL at Screening by central laboratory

   - Both HBeAg positive and negative subjects are eligible to participate

2) CPT score (Appendix 7) of 7-12 (inclusive) OR a past history of CPT score ≥ 7 and any CPT score ≤ 12 at Screening

3) $eGFR_{CG}$ ≥ 30 mL/min using the Cockcroft-Gault equation {Cockcroft 1976}:

   - $eGFR_{CG}$ is calculated by:

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

     (Note: multiply estimated rate by 0.85 for women)

4.3. Exclusion Criteria

Subjects who meet **any** of the following **exclusion criteria** are not eligible to participate in the study:

All Subjects (Parts A & B):

1) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study

2) Males and females of reproductive potential who are unwilling to use an "effective", protocol-specified method(s) of contraception during the study (Appendix 5)

3) Co-infection with HCV, HIV, or HDV

   - Subjects who are HCV positive, but have a documented negative HCV RNA, are eligible

4) Prior IFN use within 6 months of Screening

5) Evidence of hepatocellular carcinoma (i.e. evidenced by imaging within 6 months of Screening)

6) Received solid organ or bone marrow transplant

7) Significant cardiovascular, pulmonary, or neurological disease in the opinion of the investigator

8) Malignancy within 5 years prior to Screening, with the exception of specific cancers that are cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are not eligible

9) Currently receiving therapy with immunomodulators (e.g. corticosteroids), nephrotoxic agents, or agents capable of modifying renal excretion

10) Known hypersensitivity to study drugs, metabolites, or formulation excipients

11) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

12) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.

13) Use of investigational agents within 3 months of Screening, unless allowed by the Sponsor

14) Use of any prohibited medication as described in Section 5.3.

Part A Only (renal impairment):

1) Current or historical evidence of clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage)

2) Abnormal hematological and biochemical parameters, including:

   - Hemoglobin < 9 g/dL
   - Absolute neutrophil count < 750/mm^3
   - Platelets ≤ 50,000/mm^3
   - AST > 10 × ULN

- Albumin < 3.0 g/dL
- Total bilirubin > 2.5 × ULN
- INR > 1.5 × ULN (unless stable on anticoagulant regimen)

3) Subjects with ESRD (i.e. eGFR < 15 mL/min) not on HD, or those on other forms of renal replacement therapy (i.e. peritoneal dialysis)

Part B Only (hepatic impairment):

1) Active variceal bleeding within 6 months or prior placement of a portosystemic shunt (such as transjugular intrahepatic portosystemic shunt [TIPS])

2) History of hepatorenal syndrome, hepatopulmonary syndrome, Grade 3 or Grade 4 hepatic encephalopathy, or spontaneous bacterial peritonitis within 6 months of Screening

3) Grade 2 hepatic encephalopathy at Screening

4) MELD score ≥ 30

5) Abnormal hematological and biochemical parameters, including:

- Absolute neutrophil count < 750/mm^3
- Platelets < 30,000/mm^3
- Hemoglobin < 8.0 g/dL

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of TAF

5.1.1. Formulation

5.1.1.1. TAF Tablets

TAF 25 mg tablets contain 28 mg of tenofovir alafenamide fumarate, which is equivalent to 25 mg of TAF. The tablets are yellow, round-shaped, and film-coated. The tablets are debossed with "GSI" on one side and "25" on the other side. In addition to the active ingredient, each film-coated tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.1.2. Packaging and Labeling

TAF tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration. (FDA), EU Guideline to Good Manufacturing Practice − Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.1.3. Storage and Handling

TAF tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2. Dosage and Administration of Tenofovir Alafenamide (TAF)

All subjects will receive TAF 25 mg QD. It is preferred that subjects take their study drug according to a morning dosing schedule; however, evening dosing is allowable.

All study drugs should be taken at approximately the same time each day with food.

Study drug should be administered after assessing adverse events and concomitant medication(s).

On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.

CCI [redacted]

5.3. Prior and Concomitant Medications

Concomitant/previous medications **taken within 30 days of Screening**, up to and including the date of the last study visit, need to be recorded in the source documents and eCRFs.

The following medications are excluded while subjects are participating in the study. These medications are **prohibited during the Screening period and for a minimum of 30 days prior to the Baseline/Day 1** visit through the end of treatment:

- Investigational agents or devices for any indication
- Nephrotoxic agents (e.g., aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Probenecid
- Agents that reduce renal function or compete for active tubular secretion with tenofovir (e.g., cidofovir, acyclovir [except for short term (< 2 weeks) acute treatment], valacyclovir [except for short term (< 2 weeks) acute treatment], ganciclovir, valganciclovir, and multiple or high dose nonsteroidal antiinflammatory agents [NSAIDs])
- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use], immunosuppressant, or immunomodulating agents

Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters i.e., P-glycoprotein [P-gp]) with TAF may decrease TAF plasma concentrations, which may lead to loss of therapeutic effect.

Examples of representative medications which are prohibited from 21 days prior to Day 1 through the end of treatment are listed below:

Table 5-1. Disallowed Concomitant Medications

Medication Class	Prohibited Medications
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antimycobacterials	Rifapentine, Rifabutin, Rifampin
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)

Drugs that strongly inhibit P-gp and BCRP activity may increase TAF plasma concentrations. (USPI Vemlidy® {VEMLIDY® 2016}). In accordance with the EU SmPC for TAF, the use of strong P-gp inhibitors is not recommended {Vemlidy 2017}.

Should subjects have a need to initiate treatment with any excluded concomitant medication, including herbal/natural products/therapies, and over the counter medications, the Gilead Sciences Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication.

5.4. Accountability for Tenofovir Alafenamide (TAF)

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product (IMP) bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP bottles dispensed to subjects must be returned to the site.

Investigational product accountability records will be provided to each study site to:

- Record the date received and quantity of IMP bottles
- Record the date, subject number, subject initials, the IMP bottle number dispensed
- Record the date, quantity of used and unused IMP bottles returned, along with the initials of the person recording the information.

5.4.1. Investigational Medicinal Product Return or Disposal

At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. A copy of the site's SOP will be obtained for central files. Where possible, study drug will be destroyed at the site. Upon study completion, a copy of the Investigational Drug Accountability records must be filed at the site. Another copy will be returned to Gilead Sciences. If drug is destroyed on site, the investigator must maintain accurate records for all study drug bottles destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment. Once consent has been obtained, all screening tests and procedures have been completed, and study eligibility has been confirmed, subjects will begin study treatment within 45 days at the Baseline visit.

Candidates who fail to meet eligibility criteria by screening evaluations may be re-screened once after the initial screen if there is a reasonable expectation that the candidate will be eligible after repeat screening.

Retesting of an exclusionary laboratory value during the Screening period is permitted only if in the Principal Investigator's opinion, the retest value will be within accepted parameters; if the initial value was deemed to be inaccurate, inconsistent with the subject's previous result(s); in error (e.g. mishandled sample); or due to an extenuating circumstance.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 45 days before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Review of inclusion/exclusion criteria
- Obtain medical history (including HBV disease and treatment history)
- Review concomitant medications
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form
- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature), body weight, and height
- ECG (subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)

- DXA scan of hip and spine. The Baseline DXA scan can be performed at any time during the Screening period, but should be conducted at least 14 days prior to the first dose of study drug to ensure an acceptable pre-dose DXA scan.

- Obtain blood samples for:

  — plasma HBV DNA (must be < 20 IU/mL by central laboratory at time of Screening to be eligible)

  — Serum chemistry and liver function tests (including PT/INR), hematology (including ALT [must be ≤ 10 times ULN by central laboratory]), serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG,}$ HIV, HDV, HCV, serum pregnancy test (for females of child-bearing potential), α-fetoprotein (AFP). An AFP > 50 ng/mL at Screening must have an appropriate evaluation (e.g., CT scan if not performed within the previous 6 months) in order to rule out HCC prior to being permitted to enter the study.

- Urine sample for urinalysis and drug screen for all subjects except only where available for subjects in Part A, Cohort 2 (ESRD subjects on HD)

- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only

- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Baseline Assessments

All baseline tests and procedures must be completed prior to the receipt of the first dose of study drug. Subjects screened within 45 days before Baseline will be eligible to participate in the study. Initiation of treatment with study drug should take place on the day of the Baseline visit. The following will be performed at the Baseline visit:

- Review of inclusion/exclusion criteria and confirm medical history (including HBV disease and treatment history)

- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight

- Review concomitant medications

- Review adverse events
- Serum Cystatin C testing for eGFR by CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] (cystatin C)
- Blood sample for Fibrotest®
- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only
- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Complete the "Fracture Risk Assessment" (FRAX®) eCRF
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- Blood sample for serum chemistry and liver function tests (including PT/INR), hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG,}$ virology (resistance surveillance), serum and plasma for storage, sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), and vitamin D assessment
- CCI [redacted]
- Health Related Quality of Life (HRQoL) Surveys (CLDQ, SF-36, WPAI, EQ-5D-3L)
- Site-administered questions for Health Utilization Assessment to be completed
- Dispense study drug; subjects should be reminded that dosing of study drug will occur in-clinic at the next visit and/or (for Part A, Cohort 2 subjects [ESRD on HD]) after the hemodialysis at or following the next visit

6.3. Treatment Assessments

6.3.1. Week 4 (Visit Window ± 3 days)

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, $eGFR_{CG}$, virology (resistance surveillance), and serum and plasma for storage
- Blood samples for Sparse PK:
  - All subjects except Part A, Cohort 2 (ESRD subjects on HD)
    - Study drug administered in clinic and the single plasma PK sample collected between 15 minutes and 4 hours post dose
  - Part A, Cohort 2 Subjects (ESRD subjects on HD at selected sites)
    - On the day of hemodialysis, 4 samples will be collected:
      - 1 sample collected within 10 minutes before a hemodialysis session begins
      - 1 sample each collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer and
      - 1 sample collected within 10 minutes after a hemodialysis session concludes

    On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.
- CCI for **Optional Intensive PK substudy (separate consent required)**

CCI

- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Fasting blood sample for serum bone biomarkers − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense study drug; subjects should be reminded that dosing of study drug will occur in-clinic at the next visit and/or (for Part A, Cohort 2 subjects [ESRD on HD]) after the hemodialysis at or following the next visit

6.3.2. Week 8 (Visit Window ± 3 days)

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events

- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, $eGFR_{CG}$, virology (resistance surveillance), and serum and plasma for storage
- Blood samples for Sparse PK:
  - All subjects except Part A, Cohort 2 (ESRD subjects on HD)
    - Study drug administered in clinic and the single plasma PK sample collected between 15 minutes and 4 hours post dose
  - Part A, Cohort 2 Subjects (ESRD subjects on HD at selected sites)
    - On the day of hemodialysis, 4 samples will be collected:
      - 1 sample collected within 10 minutes before a hemodialysis session begins
      - 1 sample each collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer and
      - 1 sample collected within 10 minutes after a hemodialysis session concludes

      On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.
- CCI for **Optional Intensive PK substudy (separate consent required)**

- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense study drug; subjects should be reminded that dosing of study drug will occur in-clinic at the next visit and/or (for Part A, Cohort 2 subjects [ESRD on HD]) after the hemodialysis at or following the next visit

6.3.3. Week 12 (Visit Window ± 3 days)

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), and serum and plasma for storage

- Blood samples for Sparse PK:

  — All subjects except Part A, Cohort 2 (ESRD subjects on HD)

    ■ Study drug administered in clinic and the single plasma PK sample collected between 15 minutes and 4 hours post dose

  — Part A, Cohort 2 Subjects (ESRD subjects on HD at selected sites)

    ■ On the day of hemodialysis, 4 samples will be collected:

      ○ 1 sample collected within 10 minutes before a hemodialysis session begins

      ○ 1 sample each collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer and

      ○ 1 sample collected within 10 minutes after a hemodialysis session concludes

    On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.

- CCI for **Optional Intensive PK substudy (separate consent required)**

- Fasting blood sample for serum bone biomarkers − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense study drug; Part A, Cohort 2 subjects (ESRD on HD) should be reminded that dosing of study drug will occur after the hemodialysis at or following the next visit

6.3.4. Week 24 (visit window is −7 days)

- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests (including PT/INR), hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), vitamin D assessment, and serum and plasma for storage

- Blood samples for Sparse PK:
  - All subjects except Part A, Cohort 2 (ESRD subjects on HD)
    - Single plasma PK sample
  - Part A, Cohort 2 Subjects (ESRD subjects on HD at selected sites)
    - On the day of hemodialysis, 4 samples will be collected:
      - 1 sample collected within 10 minutes before a hemodialysis session begins
      - 1 sample each collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer and
      - 1 sample collected within 10 minutes after a hemodialysis session concludes

      On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.
- Blood sample for Fibrotest®
- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only
- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only
- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- DXA scan of hip and spine (within −14 days of the expected visit date)
- Health Related Quality of Life (HRQoL) Surveys (CLDQ, SF-36, WPAI, EQ-5D-3L)
- Site-administered questions for Health Utilization Assessment to be completed
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.

- Perform study drug accountability
- Dispense study drug

6.3.5. Week 36 (Visit Window ± 14 days)

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 subjects [ESRD subjects on HD]), and serum and plasma for storage
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense study drug

6.3.6. Week 48 (Visit Window is −7 days)

- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests (including PT/INR), hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), vitamin D assessment, and serum and plasma for storage

- Blood sample for Fibrotest®
- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only
- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only
- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- DXA scan of hip and spine (within −14 days of the expected visit date)
- Health Related Quality of Life (HRQoL) Surveys (CLDQ, SF-36, WPAI, EQ-5D-3L)
- Site-administered questions for Health Utilization Assessment to be completed
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- ECG (subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Perform study drug accountability
- Dispense study drug
- CCI [redacted]

6.3.7. Week 60 (Visit Window ± 14 days)

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications

- Review adverse events
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), and serum and plasma for storage
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.
- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense open label study drugs

6.3.8. Week 72 (Visit Window ± 14 days)

- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight
- Review concomitant medications
- Review adverse events
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), and serum and plasma for storage
- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD)− no food or drinks, except water, at least 8 hours prior to blood collection
- DXA scan of hip and spine (within ± 14 days of the expected visit date)
- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.

- Site-administered questions for Health Utilization Assessment to be completed
- Perform study drug accountability
- Dispense study drug

6.3.9. Week 96 (Visit Window is −7 days)

- Complete physical examination with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight
- Review concomitant medications
- Review adverse events
- ECG (subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)
- Blood sample for serum chemistry and liver function tests (including PT/INR), hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), and serum and plasma for storage
- Blood sample for Fibrotest®
- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only
- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only
- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers for all subjects except Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection
- DXA scan of hip and spine (within - 14 days of the expected visit date)
- Health Related Quality of Life (HRQoL) Surveys (CLDQ, SF-36, WPAI, EQ-5D-3L)
- Site-administered questions for Health Utilization Assessment to be completed

- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.

- Perform study drug accountability

- CCI [redacted]

6.4. Post-Treatment Assessments

6.4.1. HBsAg Loss and Seroconversion Subjects

Subjects in Part A (renally impaired) who discontinue study drug due to HBsAg loss with confirmed seroconversion to anti-HBs on or after the Week 24 visit, will be followed off treatment every 4 weeks for 12 weeks and then per the original study visit schedule through Week 96/ED (excluding drug dispensation and accountability). Discontinuation of study drug for subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or compensated cirrhosis, should be considered on a case by case basis.

Subjects with moderate or severe hepatic impairment (Part B) who experience HBsAg loss and seroconversion to anti-HBs should not discontinue study drug.

6.4.2. All Other Subjects Who Discontinue Study Drug

Subjects in Part A (renally impaired) who have received at least one dose of study drug and permanently discontinue study drug for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or up to initiation of appropriate, alternative HBV therapy, whichever occurs first. Use of appropriate, alternative HBV therapy is strongly encouraged.

For subjects in Part B (hepatic impairment) who permanently discontinue study drug, immediate initiation of appropriate, alternative HBV therapy is strongly recommended.

6.4.3. Treatment-Free Follow Up Visit Assessments (Part A Subjects)

- Symptom directed physical exam

- Body weight

- Vital signs: blood pressure, pulse, respiration rate, and temperature

- Review concomitant medications

- Review adverse events

- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA levels, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, and serum for storage

- Urine for urinalysis

6.5. Early Discontinuation (ED)/Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator.

The assessments at the unscheduled visits are at the investigator's discretion. At all unscheduled visits initiated for the purpose of confirming virologic rebound a serum blood sample for resistance testing must be collected.

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.6, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

The ED Visit should be performed within 72 hours (i.e., visit window is + 3 days) of the last study drug dose.

- Complete physical exam with vital signs (blood pressure, pulse, respiration rate and temperature) and body weight

- ECG (subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording)

- DXA scan of spine and hip to be performed within ± 14 days of the expected visit date and is done only if not done within the past 12 weeks of the ED visit

- Review concomitant medications

- Review adverse events

- Fasting blood sample for serum bone biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection (only collected if not done in the last 12 weeks)

- Fasting urine sample for renal biomarkers for all subjects except for Part A, Cohort 2 (ESRD subjects on HD) − no food or drinks, except water, at least 8 hours prior to blood collection(only collected if not done in the last 12 weeks)

- Blood sample for serum chemistry and liver function tests (including PT/INR), hematology, plasma HBV DNA level, serum HBsAg (quantitative), HBV serology (qualitative HBsAg and HBeAg), $eGFR_{CG}$, virology (resistance surveillance), sparse plasma PK (all subjects except Part A, Cohort 2 [ESRD subjects on HD]), and serum and plasma for storage

- Blood sample for Fibrotest®

- CPT ([Appendix 7] Assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment) for Part B subjects (hepatic impairment) only

- MELD Score (Assessment requires: total bilirubin, serum creatinine, serum sodium, and PT/INR) for Part B subjects (hepatic impairment) only

- Urine sample (for all subjects except only where available for subjects in Part A, Cohort 2 [ESRD subjects on HD]) for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, or if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD], a serum pregnancy test will be done), and for storage.

- Health Related Quality of Life (HRQoL) Surveys (CLDQ, SF-36, WPAI, EQ-5D-3L) are done only if not done within the past 24 weeks of the ED visit

- Site-administered questions for Health Utilization Assessment to be completed

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.

- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Therapeutic failure

- Part A (renally impaired) subjects only - HBsAg loss with seroconversion to anti-HBs. These subjects should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion before Week 24 are not permitted to discontinue study drug prior to the Week 24 visit.

- Discontinuation of study drug for subject experiencing HBsAg-loss with confirmed seroconversion to anti-HBs, who have known bridging fibrosis or cirrhosis, should be considered on a case by case basis

- Any subject with $eGFR_{CG}$ < 15 ml/min who does not initiate hemodialysis or initiates other forms of renal support (e.g. peritoneal dialysis) will be required to discontinue study treatment
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.7. Other Evaluations

6.7.1. Bone and Renal Markers

The following biological specimens will be collected in this study. The specific analyses will include, but will not be limited to, the biomarkers listed below.

- Urine Biomarkers including, but not limited to, retinol binding protein (RBP) and beta-2 microglobulin (for all subjects except Part A, cohort 2 [ESRD subjects on HD])
- Serum Bone Biomarkers including, but not limited to, C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP)

These specimens will be collected in a fasted state at Baseline and Weeks 4, 12, 24, 48, 72, and 96/ED. Samples may be stored by Gilead Sciences for a period of up to 15 years at the end of the study.

CCI [redacted]

6.7.2. Intensive Pharmacokinetic Substudy (Optional)

CCI [redacted]

CCI [redacted]

6.8. Resistance Surveillance and Virologic Rebound Management

Sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) for potential resistance mutations may be attempted for any subject with HBV DNA ≥ 69 IU/mL at Baseline and for subjects who experience viremia (HBV DNA ≥ 69 IU/mL) at Weeks 24, 48, and 96/ED. Phenotypic analysis will be performed for subjects that are subjected to sequence analysis.

As it may not be known at the time of the visit whether a patient is viremic or if it will be their last study visit, a separate serum sample for potential resistance surveillance will be collected at each study visit.

In the event of unconfirmed virologic rebound (HBV DNA ≥ 20 IU/mL), subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw. For virologic rebound occurring within the first 12 weeks of the study, the next scheduled visit will used for follow up. For virologic rebound occurring after Week 12, the subject will return for an unscheduled visit within 2-3 weeks after the date of the original test that resulted with HBV DNA virologic rebound for confirmation of virologic rebound. At this follow up visit, a serum blood sample for resistance testing will be obtained. For unscheduled visits, the subject will be required to bring their supply of study drug with them and be assessed for adherence by pill count, and if necessary, the subject will be re-counseled on adherence to study medication.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

7.2.2. Assessment of Severity

Severity of adverse events is to be determined based on GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event: both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

  Gilead DSPH: Fax: PPD
  Email: PPD

  Medical Monitor: PPD
  Phone: PPD
  Fax: PPD
  Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).
- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.
- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.
- Administration of study drug may be discontinued due to a clinical or laboratory event. The Gilead Medical Monitor should be consulted prior to dose discontinuation of study drug unless the investigator believes that immediate action is warranted to ensure the continued safety of subject.
- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue investigational medicinal product at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 CK after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.5.4. Management of Bone Evaluation

As there is uncertainty surrounding the clinical significance and management of decreases in bone mineral density for chronic HBV-infected patients, Gilead recommends that any subject who has a DXA scan that demonstrates a decrease from baseline of > 5% in bone mineral density of the spine region or the hip region be followed per local medical practice at the discretion of the investigator.

7.5.5. On-Treatment ALT Flare and Post-Treatment Exacerbation of Hepatitis Management

On-Treatment ALT Flare is defined as:

- Confirmed (within 3 days of receipt of initial laboratory results) serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms

7.5.5.1. Management of ALT Flare in Subjects Receiving Study Medication

If laboratory results indicate elevation of ALT > 2 × baseline and > 10 × ULN, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

- Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and serum albumin.

- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg and HBsAb), HDV, HAV IgM, HCV, and HEV.

Based on the results of the confirmatory tests, the following treatment modifications are recommended:

Elevated Liver Enzymes, Normal or Stable Relative to Baseline Liver Function Tests

If ALT levels are elevated (i.e., > 2 × baseline and > 10 × ULN) with normal or stable total bilirubin and INR relative to baseline, the subject may remain on study medication and should be monitored weekly as long as ALT levels return to normal or baseline level.

During monitoring, if the ALT values remain persistently elevated, the investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on commercially available HBV therapy following study drug discontinuation.

Elevated Liver Enzymes, Elevated Liver Function Tests

If ALT values are elevated (i.e., > 2 × baseline and > 10 × ULN), and total bilirubin is confirmed to be 2 × baseline value, and INR is 0.5 above baseline, provided both are > ULN, the investigator should consider discontinuing study medication (upon discussion with the Gilead Medical Monitor, unless the safety of the subject is of immediate concern).

The subject should be monitored weekly as long as ALT, total bilirubin, and INR values remain elevated or above baseline values.

During monitoring, if the ALT values and the liver function tests remain persistently elevated, the investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on commercially available HBV therapy following study drug discontinuation.

7.5.5.2. Management of Exacerbation of Hepatitis in Subjects Who Have Discontinued Study Medication

If laboratory results indicate (1) an ALT elevation > 2 × baseline and > 10 × ULN alone OR associated with (2) abnormal laboratory parameters suggestive of worsening hepatic function (total bilirubin 2 × baseline, INR 0.5 above baseline, provided both are > ULN) and the subject is on no post-study therapy for HBV, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.

- Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, creatinine, sodium, and albumin.

- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg and HBsAb), HDV, HAV IgM, HCV and HEV. If Plasma HBV DNA is increasing, the investigator should consider immediate initiation of approved therapy.

- The subject should be followed until laboratory parameters (ALT, total bilirubin, INR) return to normal or baseline up to a maximum of 6 months after the initial occurrence of the event.

7.5.6. Management of Potential Nephrotoxicity

For subjects with moderate or severe renal impairment (Part A, Cohort 1), and subjects with hepatic impairment (Part B), $eGFR_{CG}$ will be followed post-baseline during the study.

$eGFR_{CG}$ is calculated by:

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

(Note: multiply estimated rate by 0.85 for women)

Any subject with a post baseline $eGFR_{CG} < 15$ mL/min must have serum creatinine measured again within 3 calendar days of receipt of results. At the time of this repeat serum creatinine assessment, serum Cystatin C will also be measured and the eGFR by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement. Any subject who has an $eGFR_{CG}$ < 15 mL/min who also experiences > 20% reduction in eGFR by CKD-EPI (cystatin C) from baseline or any subject who has other clinical and/or laboratory evidence of acute renal failure will be discussed with the Medical Monitor and may require discontinuation from study drugs.

CKD-EPI (cystatin C) formula adjusted for age and sex:

$$eGFR\ (mL/min/1.73m^2) = 133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age}$$
[× 0.932 if female],

where Scys is serum cystatin C (mg/L), min (Scys/0.8,1) indicates the minimum of Scys/0.8 or 1, and max (Scys/0.8,1) indicates the maximum of Scys/0.8 or 1.

If the $eGRF_{CG}$ is confirmed to be < 15 ml/min and hemodialysis is to be initiated, the subject can remain on study after discussion with the Medical Monitor. However, any subject with eGFR < 15 mL/min who does not initiate hemodialysis, or those who initiate other forms of renal support (e.g. peritoneal dialysis) will be required to permanently discontinue study drug.

All subjects with moderate or severe renal impairment with a change from baseline serum creatinine of ≥ 0.4 mg/dL must have serum creatinine repeated, with a concurrent urinalysis and urine chemistry, within 2 weeks of receipt of results. If a subject has a confirmed change from baseline serum creatinine of ≥ 0.4 mg/dL, the Medical Monitor should be notified and a consultation with a nephrologist should be obtained.

All subjects with moderate or severe renal impairment with negative or trace proteinuria at baseline that develop ≥ 1+ proteinuria on urinalysis are recommended to have a urinalysis repeated, with a concurrent urinalysis and urine chemistry, within 2 weeks of receipt of results. Any subject with ≥ 1+ proteinuria at baseline who develops a ≥ 1+ change from baseline should follow this same procedure. Upon confirmation of new proteinuria, subjects will be asked to return to the clinic for a scheduled or unscheduled follow up visit for evaluation. It is recommended that the Investigator contact the Gilead Medical Monitor to discuss if further consultation with a nephrologist is clinically warranted.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, and pregnancy reports regardless of an associated AE and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure with an AE is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:

Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number PPD or email PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.6.2 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this switch study are as follows:

- To evaluate the safety and tolerability of TAF 25 mg QD at Week 24
- To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Week 24

The secondary objectives of this switch study are as follows:

- To evaluate the safety and tolerability of TAF 25 mg QD at Weeks 48 and 96
- To measure the proportion of subjects achieving virologic response (HBV DNA < 20 IU/mL) at Weeks 48 and 96
- To evaluate biochemical (ALT normal and ALT normalization) and serological (loss of HBeAg with seroconversion to anti-HBe in HBeAg-positive subjects and loss of HBsAg with seroconversion to anti-HBs) responses at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on renal parameters at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment and hepatically impaired subjects
- To evaluate the safety of TAF 25 mg QD as determined by percentage change in hip and spine bone mineral density (BMD) at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on fibrosis as assessed by Fibrotest® at Weeks 24, 48, and 96
- To evaluate the effect of TAF 25 mg QD on changes in Child-Pugh-Turcotte (CPT) and Model for End-stage Liver Disease (MELD) scores at Weeks 24, 48, and 96 in hepatically impaired subjects
- To evaluate the pharmacokinetics of TAF and TFV

The exploratory objectives of this switch study are as follows:

8.1.2. Primary Endpoint

- The primary safety endpoint is the incidence of graded adverse events and graded laboratory abnormalities at Week 24.
- The primary efficacy endpoint is the proportion of subjects achieving virologic response (plasma HBV DNA < 20 IU/mL) at Week 24.

8.1.3. Secondary Endpoint

The Secondary safety endpoints are:

- Incidence of graded adverse events and graded laboratory abnormalities at Week 48 and 96
- Change from baseline in $eGFR_{CG}$ at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment and hepatically impaired subjects
- Percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24, 48, and 96

The Secondary efficacy endpoints are:

- Proportion of subjects achieving virologic response (plasma HBV DNA < 20 IU/mL) at Weeks 48 and 96
- Proportion of subjects with plasma HBV DNA < 20 IU/mL and target detected/not detected (i.e. < LLOD) at Weeks 24, 48, and 96
- Proportion of subjects with serological response (loss of HBsAg and seroconversion to anti-HBs, loss of HBeAg and seroconversion to anti-HBe in HBeAg-positive subjects) at Weeks 24, 48, and 96
- Proportion of subjects with biochemical response (normal ALT and normalized ALT) at Weeks 24, 48, and 96
- Change in fibrosis as assessed by FibroTest® at Weeks 24, 48, and 96
- Change from baseline in CPT score (Appendix 7) and MELD score at Weeks 24, 48, and 96 in hepatically impaired subjects

8.1.4. Other Endpoints of Interest

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8.2. Analysis Conventions

If not otherwise specified, subjects will be analyzed according to the Part (and Cohort, for Part A) they enrolled into. In addition, for Part A, overall summary of Cohort 1 and Cohort 2 combined will also be provided. No combined summary of Part A and Part B will be provided.

- **Part A, Cohort 1:** Moderate (30 mL/min ≤ $eGFR_{CG}$ ≤ 59 mL/min) or severe (15 mL/min ≤ $eGFR_{CG}$ < 30 mL/min) renal impairment
- **Part A, Cohort 2:** ESRD (eGFR < 15 mL/min) maintained on HD
- **Part B:** Moderate (CPT Class B [Appendix 7]; Score of 7-9 inclusive) or Severe (CPT Class C; Score of 10-12 inclusive) hepatic impairment

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), defined as all subjects who are enrolled and received at least one dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set, defined as all subjects who are enrolled and received at least one dose of study drug.

All data collected during treatment will be included in the safety summaries.

8.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who have received at least one dose of study medication and for whom concentration data of any analytes of interest are available. The PK analysis set will be used for analyses of concentration data.

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8.2.1.4. Biomarkers

The Biomarker analysis set will include all subjects who have evaluable biomarkers data.

8.2.1.5. DEXA

8.2.1.5.1. Hip DXA Analysis Set

The Hip DXA Analysis Set includes all subjects who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline hip BMD values.

8.2.1.5.2. Spine DXA Analysis Set

The Spine DXA Analysis Set includes all subjects who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline spine BMD values.

8.3. Data Handling Conventions

For categorical efficacy endpoints, missing data will be handled using a M = F approach. Sensitivity analyses will be performed using a missing = excluded (M=E) approach.

For secondary safety endpoints of change from baseline in $eGFR_{CG}$ and percent change from baseline in hip and spine bone mineral density (BMD), an analysis will be performed using the last observation carried forward (LOCF) method to impute missing data.

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, age, etc.

Baseline data will include a summary of body weight, height, body mass index (BMI), HBV DNA level, years positive for HBV, ALT level (≤ ULN, > ULN), previous TDF use and other oral nucleoside/nucleotide treatment experience, previous interferon experience, fibrotest score, CPT and MELD score, and HBV genotype by history, if available.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary analysis will be performed when the last subject has completed Week 24 assessments or discontinued prematurely.

The proportion of subjects with plasma HBV DNA < 20 IU/mL will be summarized descriptively using an M = F approach.

8.5.2. Secondary Analyses

Continuous secondary endpoints will be summarized using conventional descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

Categorical secondary endpoints will be summarized by number and percentage of subjects that meet the endpoint. Missing data will be handled by the M = F approach. Sensitivity analyses will be performed for the primary endpoint using M = E approach.

8.6. Safety Analysis

All safety data collected on or after the date that IMP was first dispensed up to the end of treatment will be summarized. Data for the pretreatment will be included in data listings.

8.6.1. Primary Safety Analysis

Incidence of graded adverse events and graded laboratory abnormalities will be summarized. For more details, please refer to Sections 8.6.3 and 8.6.4 below.

8.6.2. Secondary Safety Analysis

The change from baseline in $eGFR_{CG}$ at Weeks 24, 48, and 96 in subjects with moderate or severe renal impairment will be summarized.

The percent change from baseline in hip and spine BMD at Weeks 24, 48, and 96 will be summarized.

8.6.3. Extent of Exposure

A subject's extent of exposure to IMP data will be generated from the IMP administration data. Exposure data will be summarized.

8.6.4. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of IMP up to the date of last dose of IMP. Continuing adverse events diagnosed prior to the start of treatment and worsening in severity grade, or non-serious adverse events at baseline which become serious, or adverse events resulting in treatment discontinuation after the start of treatment will also be considered treatment-emergent. Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided:

- Treatment-emergent adverse events
- Treatment-emergent study drug-related adverse events

- Grade 3 or 4 treatment-emergent adverse event
- Grade 3 or 4 treatment-emergent study drug-related adverse event
- Grade 2, 3, or 4 treatment-emergent adverse event
- Grade 2, 3, or 4 treatment-emergent study drug-related adverse event
- AE that caused permanent discontinuation from study drug
- AE that caused change in dose or temporary interruption of study drug
- Treatment-emergent serious adverse event
- Treatment-emergent study drug-related serious adverse event

8.6.5. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to the end of treatment will be summarized.

Laboratory abnormalities that occur before the first dose of IMP or after the subject has been discontinued from treatment will be included in a data listing.

8.7. Pharmacokinetic Analysis

In the PK analysis set, plasma concentrations of the study drug over time will be listed. Details of the analysis will be provided in the pharmacokinetic reporting and analysis plan.

In the intensive PK substudies, pharmacokinetic parameters will be listed and summarized for TAF and TFV using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.

8.8. Biomarker Analysis

Selected renal biomarkers, including retinol binding protein, beta-2 microglobulin, will be summarized for Part A, Cohort 1 (moderate or severe renal impairment) and Part B (moderate or severe hepatic impairment) by visit using descriptive statistics.

Selected bone biomarkers, including C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP), will be summarized by visit using descriptive statistics.

8.9. Sample Size

No formal sample size calculation was performed as this is an exploratory study. A sample size of 120 subjects is based on practical considerations and is considered sufficient to evaluate the primary objectives of the study.

8.10. Data Monitoring Committee

A data monitoring committee (DMC) will review the progress of the study and perform review of safety data after 30 subjects have completed 12 weeks of treatment. However, Gilead will defer to the DMC for any decision to convene earlier or more frequently. The DMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies. No formal stopping rules will be used by the DMC for safety outcomes. Rather a clinical assessment will be made to determine if the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Ethics Committee (EC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC/EC. The investigator will not begin any study subject activities until approval from the IRB/IEC/EC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from IRB/IEC/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC/EC approved consent form for documenting

written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC/EC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC/EC or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions for further details. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria (i.e., history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria]);

- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data

verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IEC/EC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC/EC in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) and/or Other Oral Antiviral Treatment (OAV) in Virologically Suppressed Chronic Hepatitis B Subjects with Renal and/or Hepatic Impairment

GS-US-320-4035, Amendment 1, 23 May 2017

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Medical Monitor

PPD

24 May 2017

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Procedures	Visit Windows[k]		± 3 Days			± 14 Days						ED[l]	Follow Up[m]
	Screening (45 days)	Baseline (Day 1)	Week 4	Week 8	Week 12	Week 24[k]	Week 36	Week 48[k]	Week 60	Week 72	Week 96[k]		
Informed Consent	x												
Inclusion/Exclusion Criteria	x	x											
Medical History (including HBV disease and treatment history)	x	x											
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete Physical Examination with weight and vital signs[a]	x	x				x		x		x	x	x	
Height	x												
Body Weight	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs[a]	x	x	x	x	x	x	x	x	x	x	x	x	x
Symptom driven Physical Examination			x	x	x		x		x				x
Health Related Quality of Life (CLDQ, SF-36, WPAI, EQ-5D-3L)[b]		x				x		x			x	x	
Health Utilization Assessment		x	x	x	x	x	x	x	x	x	x	x	
Serum Chemistry, Hematology, and Liver Function Tests[c]	x	x	x	x	x	x	x	x	x	x	x	x	x
Fasting Metabolic Assessment[d]		x				x		x		x	x	x	
Pregnancy testing (women of child-bearing potential only)	serum	urine (+ve test to be confirmed with serum; serum test will also be collected if urine cannot be collected for subjects in Part A, Cohort 2 [ESRD subjects on HD])											
	x	x	x	x	x	x	x	x	x	x	x	x	
Estimated Glomerular Filtration Rate by Cockcroft-Gault method ($eGFR_{CG}$)	x	x	x	x	x	x	x	x	x	x	x	x	x

Study Procedures	Visit Windows[k]		± 3 Days			± 14 Days						ED[l]	Follow Up[m]
	Screening (45 days)	Baseline (Day 1)	Week 4	Week 8	Week 12	Week 24[k]	Week 36	Week 48[k]	Week 60	Week 72	Week 96[k]		
HBV serology (qualitative HBsAg and HBeAg) and quantitative HBsAg[e]	x	x			x	x	x	x	x	x	x	x	x
HCV, HDV, HIV Testing	x												
α-fetoprotein (AFP)[f]	x												
Urinalysis[g]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine drug screen[g]	x												
DXA scans (Hip & Spine)[h]	x					x		x		x	x	x	
ECG[i]	x							x			x	x	
Plasma HBV DNA level	x	x	x	x	x	x	x	x	x	x	x	x	x
FibroTest®		x				x		x			x	x	
CPT and MELD Scores (Part B subjects [hepatic impairment] only)[j]	x	x				x		x			x	x	
Serum Cystatin C[n]		x											
Fasting Blood for Bone Biomarkers, Fasting Urine for Renal Biomarkers[o]		x	x		x	x		x		x	x	x	
Fracture Risk Assessment (FRAX)		x											
Virology (Sequence analysis of HBV pol/RT for resistance surveillance)[p]		x	x	x	x	x	x	x	x	x	x	x	
Vitamin D		x				x		x					
Sparse Plasma PK (All subjects except Part A, Cohort 2 [ESRD subjects on HD])[q]		x	x	x	x	x	x	x	x	x	x	x	
Sparse Plasma PK (Part A, Cohort 2 [ESRD subjects on HD])[r]			x	x	x	x							
CCI [redacted]													

Study Procedures	Visit Windows[k]		± 3 Days			± 14 Days						ED[l]	Follow Up[m]
	Screening (45 days)	Baseline (Day 1)	Week 4	Week 8	Week 12	Week 24[k]	Week 36	Week 48[k]	Week 60	Week 72	Week 96[k]		
CCI													
Serum, plasma, and urine[g] for storage		x	x	x	x	x	x	x	x	x	x	x	x (serum only)
Study Drug Accountability			x	x	x	x	x	x	x	x	x		
Study Drug Dispensation		x	x	x	x	x	x	x	x	x			
In-clinic Dosing[t]			x	x	x	x							

a Vital signs include blood pressure, pulse, respiration rate and temperature.
b Health Related Quality of Life surveys required for Early Discontinuation (ED) visit if not done within the last 24 weeks of the expected ED visit date.
c Serum chemistry and Liver Function Tests: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN), and PTH. PTH analyzed at all visits except for Screening. At Baseline, Weeks 24, 48, 72, and 96/ED, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry panel. Liver Function Tests: PT/INR will be done at Screening, Baseline, and Weeks 24, 48, and 96/ED and then as a reflex only test for ALT flares.
d Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides).
e HBeAb and HBsAb reflex testing will be performed as needed.
f An AFP > 50 ng/mL at Screening must have an appropriate evaluation (e.g., CT scan if not performed within the previous 6 months) in order to rule out HCC prior to being permitted to enter the study.
g Urine sample collection for all subjects except only where available for subjects in Part A, Cohort 2 (ESRD subjects on HD).
h The Baseline DXA can be performed at any time during the Screening period, but should be completed at least 14 days prior to the first dose of study drug to ensure an acceptable pre-dose DXA scan. The Week 24, Week 48, and Week 96 DXA window is −14 days only. DXA required for Early Discontinuation (ED) visit if not done within the last 12 weeks and should be done within ± 14 days of the expected ED visit date.
i Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
j CPT [Appendix 7] assessment requires: total bilirubin, albumin, PT/INR, Ascites assessment, and Hepatic encephalopathy assessment. MELD assessment requires total bilirubin, serum creatinine, PT/INR, and serum sodium.
k The visit window for the Week 24, Week 48, and Week 96 visits is −7 days only.
l The Early Discontinuation (ED) visit should be performed within 72 hours of the last study drug dose (+ 3 days)

m Subjects in Part A (renally impaired) who discontinue study drug due to HBsAg loss with confirmed seroconversion to anti-HBs on or after the Week 24 visit, will be followed off treatment every 4 weeks for 12 weeks and then per the original study visit schedule through Week 96/ED. Subjects in Part A (renally impaired) who have received at least one dose of study drug and permanently discontinue study drug for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or up to initiation of appropriate, alternative HBV therapy, whichever occurs first. Use of appropriate, alternative HBV therapy is strongly encouraged. For subjects in Part B (hepatic impairment) who permanently discontinue study drug, immediate initiation of appropriate, alternative HBV therapy is strongly recommended.

n Any subject with a post baseline $eGFR_{CG}$ < 15 mL/min must have serum creatinine measured again within 3 calendar days of receipt of results. At the time of this repeat serum creatinine assessment, serum Cystatin C will also be measured and the eGFR by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement. Any subjects who have an $eGFR_{CG}$ < 15 mL/min that also experience > 20% reduction in eGFR by CKD-EPI (cystatin C) from baseline or who have other clinical and/or laboratory evidence of acute renal failure will be discussed with the Medical Monitor and may discontinue from study drugs.

o Blood for selected bone biomarkers and urine for selected renal biomarkers will be collected in a fasted state. The fasting urine sample will be collected for all subjects except Part A, Cohort 2 (ESRD subjects on HD). Required for ED visit if the last sample was not collected within the last 12 weeks.

p Resistance sequence analysis may be performed at Baseline for subjects with HBV DNA ≥ 69 IU/mL and may be attempted for viremic (HBV DNA ≥ 69 IU/mL) at Weeks 24, 48, and 96/ED. Phenotypic analysis will be performed for subjects that are subjected to sequence analysis. As it may not be known at the time of the visit whether a subject is viremic or if it will be their last study visit, a virology sample will be collected as each visit. In the event of unconfirmed virologic rebound (HBV DNA ≥ 20 IU/mL), subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw. For virologic rebound occurring within the first 12 weeks of the study, the next scheduled visit will used for follow up. For virologic rebound occurring after Week 12, the subject will return for an unscheduled visit 2-3 weeks after the date of the original test that resulted with HBV DNA virologic rebound for confirmation of virologic rebound. At this follow up visit, a serum blood sample for resistance testing will be obtained. For unscheduled visits, the subject will be required to bring their supply of study drug with them and be assessed for adherence by pill count, and if necessary, the subject will be re-counseled on adherence to study medication.

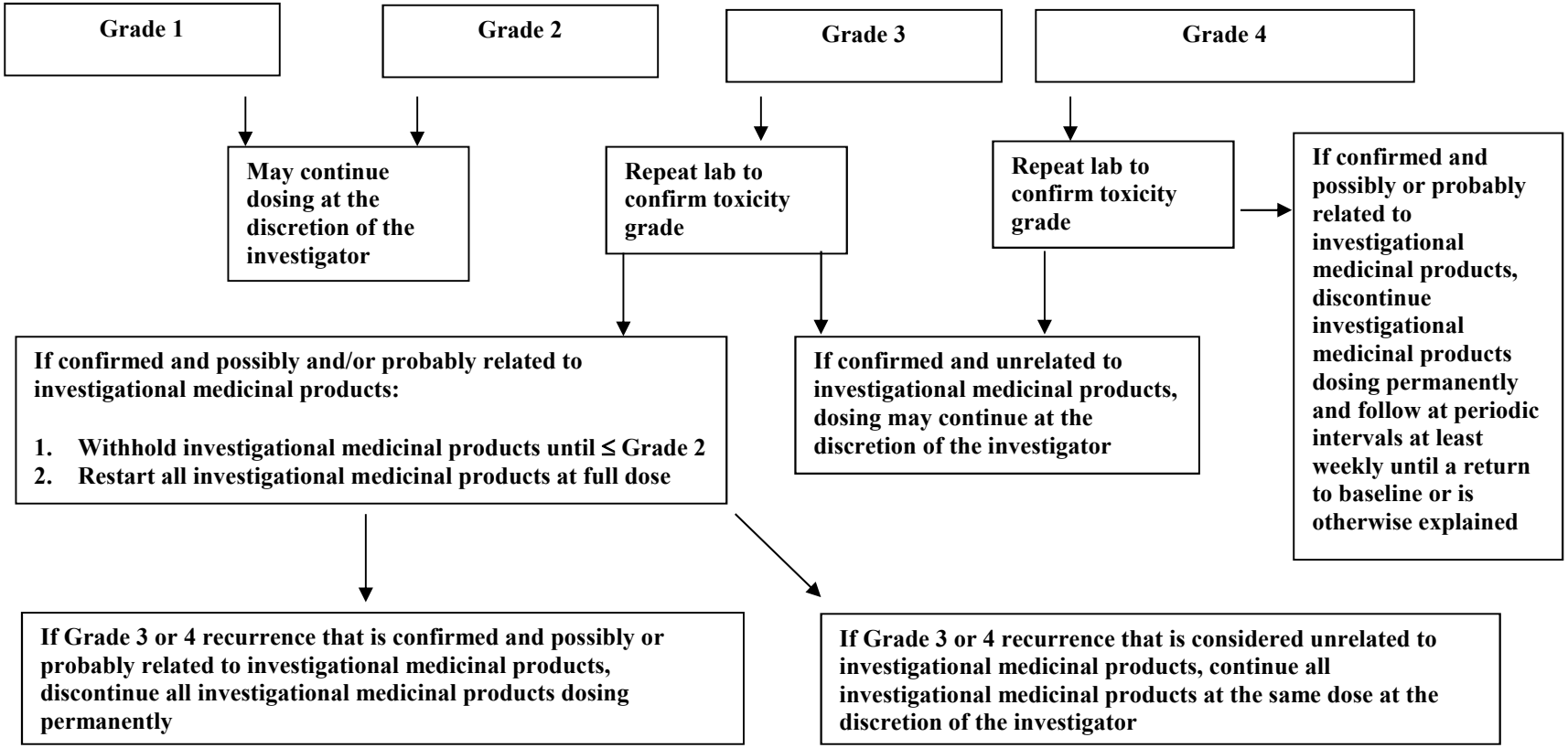
q For all subjects except Part A, Cohort 2 (ESRD subjects on HD): A single PK blood sample will be collected at Baseline and at each subsequent on treatment visit. At the Week 4, 8 and 12 visits, study drug will be administered in clinic, and the single PK blood sample will be collected between 15 minutes and 4 hours post dose.

r For Part A, Cohort 2 (ESRD subjects on HD at selected sites): 4 PK blood samples total will be collected at each of 4 hemodialysis sessions between Weeks 4 and Week 24, inclusive: one sample collected within 10 minutes before a hemodialysis session begins, one sample each collected approximately 1 hour prior to conclusion of the hemodialysis session from both the arterial and venous sides of the dialyzer, and one sample collected within 10 minutes after a hemodialysis session concludes. **On the day of hemodialysis, study drug should not be administered to subjects until after the completion of hemodialysis and collection of any required post-hemodialysis samples for Part A, Cohort 2.**

s CCI [redacted]

t Dosing of study drug will occur in-clinic at the Weeks 4, 8, and 12 visits for subjects in Part A, Cohort 1 (moderate or severe renal impairment) and Part B (hepatic impairment). CCI [redacted]

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

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
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months**[#]	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 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	>ULN to 150 mEq/L >ULN 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 **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 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 2.5 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 to < 2.5 mEq/L 2.0 t o <2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 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 > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmol/L	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 <LLN mg/dL 0.96 to <LLN mmol/L 3.5 to <LLN mg/dL 1.12 to <LLN 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
Hyperbilirubinemia **Adult and Pediatric** **> 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 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 **Adult and Pediatric** **≥ 1 year** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L < 0.5 mg/dL < 27 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 **Adult and Pediatric ≥ 4 Years**	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
Pediatric < 4 Years	NA	11.0 mEq/L to <LLN 11.0 mmol/L to <LLN	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) **Adult**	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
LDL (Fasting) **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
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

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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 **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA 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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated 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
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 weak-ness 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
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)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences 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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	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)
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 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies in animals (rats and rabbits) of TAF have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of TAF in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of < 1% per year

  — Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  — Barrier methods (one female barrier and one male barrier must be used in combination)

    ■ Female barriers: Diaphragm with spermicide or Cervical cap with spermicide

    ■ Male barriers: Male condom (with or without spermicide)

  — Hormonal methods

    ■ Oral contraceptives (either combined or progesterone only)

    ■ Injectable progesterone

    ■ Implants of levonorgestrel

    ■ Transdermal contraceptive patch

    ■ Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 6. Optional Intensive Pharmacokinetic Sub-study Recommended Meal Examples

Appendix 7. Child-Pugh-Turcotte Score {Pugh 1973}

Parameter	Points Assigned		
	1	**2**	**3**
Albumin	> 3.5 g/dL (35 g/liter)	2.8 - 3.5 g/dL (28 to 35 g/liter)	< 2.8 g/dL (< 28 g/liter)
Ascites	Absent	Slight	Moderate to Severe
Bilirubin	< 2 mg/dL (< 34.2 micromol/liter)	2 - 3 mg/dL (34.2 to 51.3 micromol/liter)	> 3 mg/dL (> 51.3 micromol/liter)
Encephalopathy	None	Grade 1 – 2	Grade 3 - 4
Prothrombin time			
Seconds over control	< 4	4 – 6	> 6
INR	< 1.7	1.7 – 2.3	> 2.3

Modified Child-Pugh-Turcotte classification of the Severity of Liver Disease

	Class A	**Class B**	**Class C**
Total Points	5-6	7-9	10-15
Severity of Hepatic Cirrhosis	Well-compensated	Significant Functional Compromise	Decompensated
1- and 2- year survival	100% and 85%	80% and 60%	45% and 35%