GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	115, 561	
EudraCT Number:	2013-000626-63	
ClinicalTrials.gov Identifier:	NCT01940341	
Indication:	HBeAg-negative Chronic Hepatitis B	
Protocol ID:	GS-US-320-0108	
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Protocol Version/Date:	Amendment 3.4:	25 September 2019

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Title of Study:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B
IND Number:	115,561
EudraCT Number:	2013-000626-63
ClinicalTrials.gov Identifier:	NCT01940341
Study Centers Planned:	Approximately 160 centers worldwide
Objectives:	The primary objectives of this study are as follows: • To compare the efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment-naïve and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL. • To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment-naïve and treatment-experienced subjects The key secondary safety objectives of this study are as follows: • To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Week 48 • To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the change from baseline in serum creatinine at Week 48

Other secondary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Weeks 96 and 144
- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL (target not detected) at Weeks 48, 96, and 144
- To compare the biochemical (ALT normalization) response of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144
- To compare the serological response (loss of HBsAg with seroconversion to anti-HBs) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144
- To compare the change in fibrosis as assessed by FibroTest® of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144
- To compare the incidence of drug resistant mutations of TAF 25 mg QD versus TDF 300 mg QD at Weeks 48, 96, and 144
- To compare the change from baseline in ophthalmologic findings by fundoscopic examination of TAF 25 mg QD versus TDF 300 mg QD at Weeks 24, 48, 72, 96, and 144 in a subset of subjects
- To characterize the pharmacokinetics of TAF and tenofovir (TFV) and determine intracellular concentrations of tenofovir diphosphate (TFV-DP) within peripheral blood mononuclear cells (PBMCs) in subjects receiving TAF or TDF
- To evaluate the comparative open-label efficacy , safety, and incidence of drug resistance mutations of TAF 25 mg QD in subjects initially randomized to TAF 25 mg QD and in subjects sequentially treated with TDF 300 mg QD and then switched to open-label TAF 25 mg QD

Study Design:

This is a randomized, double-blind, non-inferiority study to compare the antiviral activity of TAF 25 mg QD versus TDF 300 mg QD. Approximately 390 subjects will be randomized in a 2:1 ratio (A:B) to the treatment arms and will be stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, $\geq$ 7 $\log_{10}$ IU/mL < 8 $\log_{10}$ IU/mL, $\geq$ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naïve vs. treatment-experienced).

Treatment Arm A: 260 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD

Treatment Arm B: 130 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD

For China, approximately 150 additional subjects (100 in Treatment Arm A and 50 in Treatment Arm B) will be enrolled for local registration purposes.

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

Subjects with a confirmed creatinine clearance (CL_{Cr}) < 50 mL/min, and > 20 % decline in eGFR by CKD-EPI (cystatin C), at any time during the double blind period of the study will be required to undergo dose modification to every other day dosing of study drug. Subjects with confirmed creatinine clearance < 30 mL/min at any time during the study will have the study drug permanently discontinued.

The primary analysis will occur at Week 48 with the primary efficacy endpoint being the proportion of subjects with complete viral suppression, i.e., plasma HBV DNA level below 29 IU/mL.

Subjects who permanently discontinue study drug (either prematurely or at the end of study [Week 384]) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available, HBV therapy, whichever occurs first. Use of commercial therapy is strongly encouraged.

	Subjects with HBsAg loss with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion to anti-HBs prior to Week 48 are not permitted to discontinue study drug prior to the Week 48 visit. Subjects who discontinue study drug for confirmed seroconversion to anti-HBs will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule (Appendix 2) through Week 384/ED. Discontinuation of study drug for subjects experiencing HBsAg loss with confirmed seroconversion, who have known bridging fibrosis or cirrhosis, should be considered on a case by case basis. An external, independent, multidisciplinary Data Monitoring Committee (DMC) will review the progress and safety of this study approximately every 24 weeks following the time of randomization of the first subject during the double blind period of the study. During the open-label duration of the study (Weeks 144 to 384), the DMC will convene approximately every 48 weeks. At each meeting, the DMC will review routine safety and dual energy X-ray absorptiometry (DXA) data and will make recommendations regarding modification of the study treatment.
Number of Subjects Planned:	390 subjects (260 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD, and 130 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD) For China, approximately 150 additional subjects (100 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD, and 50 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD) will be enrolled.
Target Population:	Subjects, who are 18 years of age and older, with HBeAg-negative, chronic hepatitis B
Duration of Treatment:	The duration of the double-blind treatment is 144 weeks (96 weeks under Amendment 2.1). After completing the double-blind period of treatment, all subjects remaining on treatment will be eligible to receive open label TAF 25 mg QD for up to an additional 240 weeks (Week 144 through Week 384). Subjects already assigned to open-label TAF 25 mg QD at Week 96 per Amendment 2.1 will continue on open-label TAF through Week 384/ED. Subjects who lose HBsAg with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs, or after Week 48, if seroconversion occurs prior to this visit.

Diagnosis and Main Eligibility Criteria:

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

1) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
2) Male and non-pregnant, non-lactating female subjects, 18 years of age and older, 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 6).
3) Documented evidence of chronic HBV infection (e.g. HBsAg positive for more than 6 months)
4) HBeAg-negative, chronic hepatitis B with all of the following:
   a) HBeAg-negative and HBeAb positive at Screening (if the subject is deemed ineligible for this study by HBV serology [i.e. HBeAg positive CHB], this information may be used to determine eligibility for GS-US-320-0110 [another Gilead Sciences Phase 3 study in HBeAg-positive, CHB subjects; this study must also be IRB/EC approved at the participating center])
   b) Screening HBV DNA $\geq 2 \times 10^4$ IU/mL
   c) Screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and $\leq 10 \times$ ULN (by central laboratory range)
5) Treatment-naïve subjects (defined as < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue), **OR** treatment-experienced subjects (defined as subjects meeting all entry criteria [including HBV DNA and serum ALT criteria] and with ≥12 weeks of previous treatment with any nucleoside or nucleotide analogue) will be eligible for enrollment. Treatment-experienced subjects receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization, when it will be discontinued.
6) Any previous treatment with interferon (pegylated or non-pegylated) must have ended at least 6 months prior to the baseline visit.

7) Estimated creatinine clearance (CL_{Cr}) ≥ 50 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the Screening evaluation, as follows:

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

[Note: multiply estimated rate by 0.85 for women]

8) Normal ECG (or if abnormal, determined by the investigator not to be clinically significant)
9) Must be willing and able to comply with all study requirements.

Exclusion Criteria

Subjects who meet ***any*** of the following exclusion criteria are not to be enrolled in the study.

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. For a list of protocol-specified contraceptive methods, refer to Appendix 6.
3) Co-infection with HCV, HIV, or HDV
4) Evidence of hepatocellular carcinoma (e.g. as evidenced by recent imaging)
5) Any history of, or current evidence of, clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage).
6) Abnormal hematological and biochemical parameters, including:
   a) Hemoglobin < 10 g/dL
   b) Absolute neutrophil count < 750/mm^3
   c) Platelets ≤ 50,000/mm^3
   d) AST or ALT > 10 × ULN
   e) Total bilirubin > 2.5 × ULN
   f) Albumin < 3.0 g/dL
   g) INR > 1.5 × ULN (unless stable on anticoagulant regimen)
7) Received solid organ or bone marrow transplant
8) Significant renal, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator

9) Significant bone disease (eg, osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses), or multiple bone fractures
10) 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
11) Currently receiving therapy with immunomodulators (e.g. corticosteroids), investigational agents, nephrotoxic agents, or agents capable of modifying renal excretion
12) Known hypersensitivity to study drugs, metabolites, or formulation excipients
13) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
14) 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.
15) Subjects on prohibited concomitant medications (See Table 5-1). Subjects on prohibited medications, otherwise eligible, will need a wash out period of at least 30 days.

Study Procedures/ Frequency:

Laboratory analyses (serum chemistry, liver tests, hematology, urinalysis, plasma HBV DNA levels, pregnancy testing [for females of childbearing potential]), vital signs, adverse events and concomitant medications will be performed at Screening, Baseline, and every 4 weeks thereafter through Week 48, every 8 weeks through Week 96, every 12 weeks through Week 144, and every 24 weeks through Week 384/Early Discontinuation (ED) visit. HBV serology (HBeAg and HBeAb, HBsAg and reflex HBsAb [anti-HBs]) will be performed at Screening and Baseline, HBsAg and reflex HBsAb will be performed every 12-16 weeks until Week 144, every 24 weeks until Week 384/ED and at Follow Up Weeks 12 and 24. Quantitative serum HBsAg will be assessed at Screening, Baseline, and every 12-16 weeks until Week 144, every 24 weeks until Week 384/ED, and at Follow Up visits. Bone and renal biomarker testing will be performed at Baseline and then at defined intervals (see Schedule of Assessments, Appendix 2) throughout the study. IL28B polymorphism genotype, HBV genotyping and vitamin D level will be performed at Baseline only. Fibrotest® will be performed at Baseline and every 48 weeks until Week 384/ED. Fasting metabolic assessments (fasting glucose and lipid panel) will be

conducted at Baseline, every 24 weeks until Week 240, and every 48 weeks until Week 384/ED visit.

Complete physical examinations will be performed at Screening, Baseline, and Weeks 24, 48, 72, 96, 144, 240 and Week 384/ED. Height assessment will be conducted at Screening only. Symptom directed physical exams with body weight assessment will be conducted at all other visits. ECG will be performed at Screening and every 48 weeks thereafter. At sites in China with the capability only, DXA scans of the hip and spine will be conducted during the screening period, and should be conducted at least 14 days prior to the first dose of study drug, and will be subsequently conducted at Weeks 24, 48, 72, 120, 96, 144, every 48 weeks until Week 384, and the ED visit, if not done within the last 24 weeks. Hepatic ultrasound for surveillance of hepatocellular carcinoma will be performed starting at Week 96 and then every 24 weeks until Week 384/ED.

Genotypic analysis of the HBV polymerase/reverse transcriptase (pol/RT) for resistance surveillance will be performed at Baseline for all subjects and attempted for all viremic subjects (HBV DNA $\geq$ 69 IU/mL) at Weeks 48, 96, 144 and every 48 weeks until Week 384/ED. 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 virology sample for potential resistance surveillance will be collected at each study visit. Plasma, serum, and urine will be collected at Baseline and at every visit thereafter for storage.

A single pharmacokinetic (PK) blood sample will be collected at all study visits from Weeks 4 through 48 for all subjects. At the Week 4 and 12 visits, dosing will occur in-clinic and a single PK blood sample will be collected between 15 minutes and 4 hours post-dose. It is preferred that subjects take their study drug according to a morning dosing schedule; however, evening dosing is allowable. Subjects who elect to dose in evening are not required to have in-clinic dosing and the single PK blood sample collection performed at the Week 4 and 12 visits.

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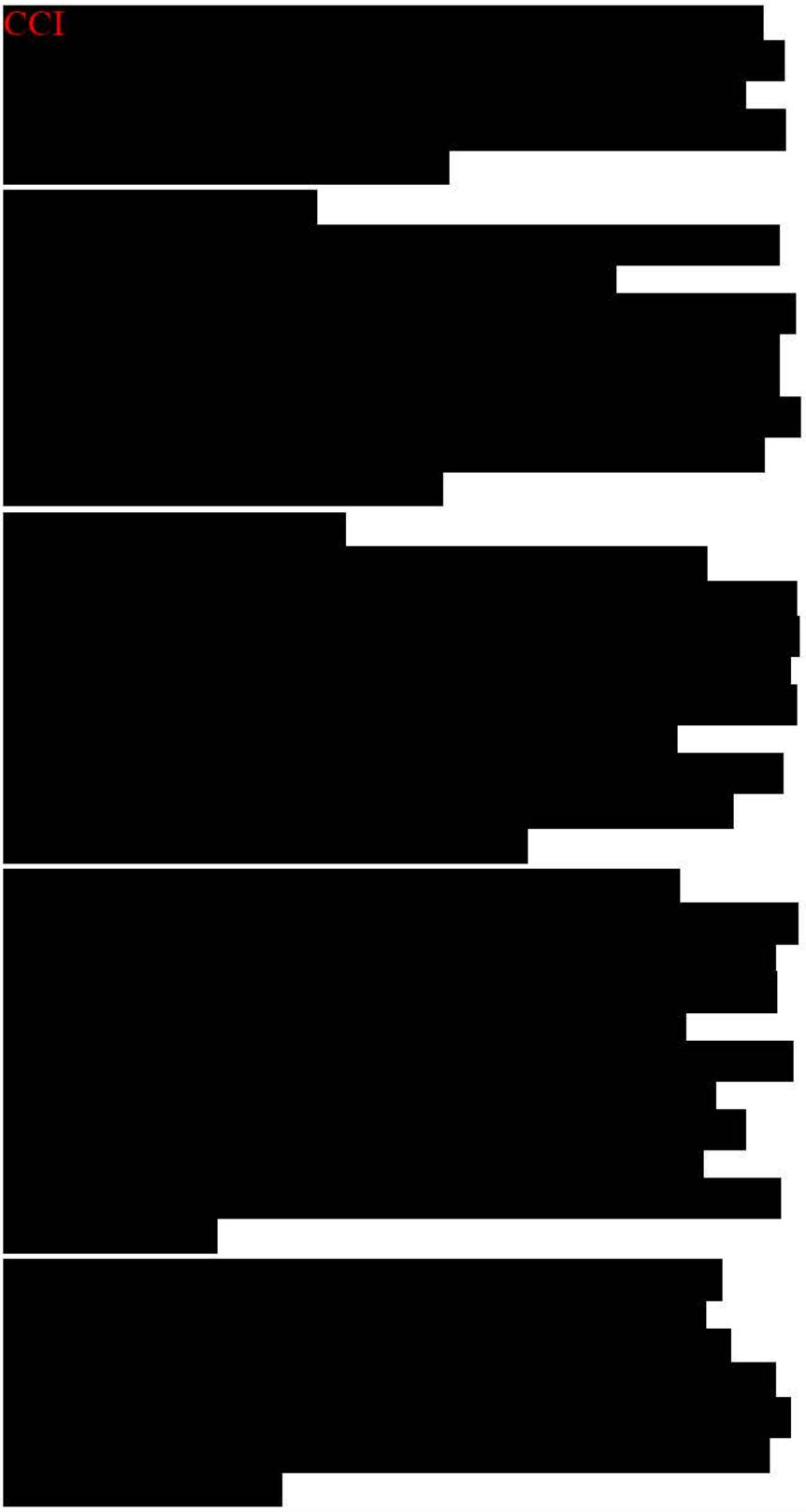


Test Product, Dose, and Mode of Administration:	Double-Blind Treatment: • Tenofovir alafenamide (TAF) 25 mg QD, oral administration and matched placebo of Tenofovir DF (TDF) 300 mg QD, oral administration Open-Label Treatment: • Tenofovir alafenamide (TAF) 25 mg QD, oral administration
Reference Therapy, Dose, and Mode of Administration:	Double-blind Treatment: • Tenofovir DF 300 mg QD, oral administration and matched placebo of Tenofovir alafenamide (TAF) 25 mg QD, oral administration Open-label Treatment: NA
Criteria for Evaluation:	
Safety:	Key secondary safety endpoints include the percent change from baseline at Week 48 in hip and spine BMD, and change from baseline at Week 48 in serum creatinine. If a subject has confirmed creatinine clearance (CL_{Cr}) < 50 mL/min, and > 20% decline in eGFR by CKD-EPI (cystatin C), at any time during the double-blind period of the study, the subject will be required to undergo dose modification to every other day dosing of study drug. Subjects with confirmed creatinine clearance < 30 mL/min at any time during the study will have the study drug permanently discontinued. The proportion of subjects in each treatment arm with tolerability failure (defined as an adverse event [AE] leading to permanent discontinuation of study drug) at Weeks 48, 96, 144, 240, and 384 will be summarized. Change from baseline in serum creatinine will be assessed at every visit and summarized through Week 384/ED. Change from baseline in BMD by DXA of the spine and hip will be assessed at Weeks 24, 48, 72, 96, 120, and 144, and every 48 weeks until Week 384/ED. Fracture Risk Assessment will be evaluated at Baseline. Ophthalmologic changes from baseline by fundoscopic examination at Weeks 24, 48, 72, 96, and 144 (or ED if prior to Week 144 and more than 24 weeks since the last exam) will be summarized for a subset of subjects (n = 30). In addition, for any subject who develops signs or symptoms of posterior uveitis, the investigator should contact the Gilead Medical Monitor to discuss the need for additional ophthalmologic evaluation including dilated fundoscopy and optical coherence tomography (OCT).

	Adverse events and clinical laboratory tests will be collected at every visit and summarized through Week144. Additionally, summaries of AEs, discontinuations due to AEs, and laboratory data including BMD measurements (via DXA scans, serum creatinine and creatinine clearance by Cockcroft-Gault) by original treatment arms (TAF versus TDF) will continue through Week 384. Fracture risk assessment will be evaluated at Baseline. In China, this fracture risk assessment will be evaluated at sites with DXA capability only.
Efficacy:	The primary efficacy endpoint is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 48. Other secondary efficacy endpoints are: • The proportion of subjects with plasma HBV DNA < 29 IU/mL at Weeks 96, 144, 240, and 384 • The proportion of subjects with plasma HBV DNA < 29 IU/mL (target not detected) at Weeks 48, 96, 144, 240, and 384 • The proportion of subjects with ALT normalization (by central laboratory and American Association for the Study of Liver Diseases [AASLD] criteria) at Weeks 48, 96, 144, 240, and 384 • The proportion of subjects with HbsAg loss at Weeks 48, 96, 144, 240, and 384 • The proportion of subjects with HbsAg seroconversion to anti-HBs at Weeks 48, 96, 144, 240, and 384 • The change from baseline in fibrosis as assessed by FibroTest® at Weeks 48, 96, 144, 240, and 384 • The incidence of drug resistant mutations at Weeks 48, 96, 144, 240, and 384
Pharmacokinetics:	The following TAF and TFV plasma pharmacokinetic parameters will be calculated for the CCI population (n = 30): C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, $AUC_{tau,}$ AUC_{last}, CL/F, V/F, λ_z and $t_{½}$ Single PK plasma samples collected at Weeks 4-48 may be used for estimation of population pharmacokinetics of TAF and TFV. Single PBMC samples at selected PK substudy sites collected at the intensive PK substudy visit will be used for TFV-DP concentration determination

Statistical Methods:	The primary analysis will be performed when approximately 390 subjects complete 48 weeks of the double-blind treatment period or discontinue prematurely. The analysis will compare the TAF arm to the TDF arm.
Analysis Methods:	A two-sided 95% confidence interval, based on large sample theory, adjusted for the randomization stratification factors, for the difference (TAF-TDF) between treatments will be evaluated to compare treatment groups with respect to the primary efficacy endpoint. A missing equals failure approach will be employed for the primary analysis. Non-inferiority will be declared if the lower bound of this confidence interval exceeds 0.10 (i.e., 10% non-inferiority margin). If non-inferiority is established, the lower bound of the 95% confidence interval (CI) will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of TAF over TDF will be established using the same CI. The percent change from baseline in hip and spine BMD at Week 48 will be analyzed using an analysis of variance (ANOVA) model. The model will include treatment group as a fixed effect. The details are provided in the Statistical Analysis Plan (SAP). The change from baseline in serum creatinine at Week 48 will be analyzed using an analysis of covariance (ANCOVA) model with baseline serum creatinine as a covariate, and treatment group as a fixed effect. The details are provided in the SAP. 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:	With respect to the primary efficacy endpoint of proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Week 48, when the sample sizes are 260 (TAF 25 mg arm) and 130 (TDF 300 mg arm), a two-group, large-sample normal approximation test of proportions with a one-sided 0.025 significance level will have 90% power to reject the null hypothesis, that the TAF 25 mg arm is inferior to the TDF 300 mg arm (the difference in proportions [TAF-TDF] having a lower bound of the one-sided 97.5% confidence interval of less than 0.10, i.e., 10%) in favor of the alternative hypothesis that the TAF 25 mg arm is not inferior to the TDF 300 mg arm. This assumes the expected difference (TAF-TDF) in proportion of

subjects with HBV DNA < 29 IU/mL is 0 and the proportion of subjects with HBV DNA < 29 IU/mL in the TDF 300 mg arm is 0.91.

The TDF virologic rate of 0.91 was calculated using the observed rate in Study GS-US-174-0102.

This sample size also provides 90% power to detect a 1% difference in the percentage change from baseline in hip BMD at Week 48 (assuming a 1.17% change from baseline in TDF 300 mg arm and 0.17% change in TAF 25 mg arm, with a common standard deviation of 2.20% and a two-sided $\alpha = 0.025$); a 77% power to detect a 1% difference in the percentage change from baseline in spine BMD at Week 48 (assuming a 1.69% change from baseline in the TDF 300 mg arm and 0.69% change in the TAF 25 mg arm, with a common standard deviation of 3.08% and a two-sided $\alpha = 0.025$); a 52% power to detect a 0.03 mg/dL difference in the change from baseline in serum creatinine at Week 48 (assuming a 0.04 mg/dL change from baseline in the TDF 300 mg arm and 0.01 mg/dL change from baseline in the TAF 25 mg arm, with a common standard deviation of 0.12). These assumptions were derived from studies GS-98-437, GS-98-438, GS-US-174-0102, GS-US-174-0103, and GS-US-174-0121.

For China, approximately 150 additional subjects (100 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD, and 50 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD) will be enrolled.

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
AhR	Aryl hydrocarbon receptor
AK	Adenylate kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Adverse reaction
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)
bsAP	Bone specific alkaline phosphatase
BMD	Bone mineral density
CatA	Cathepsin A
CD4	Cluster of differentiation 4 cells
CD8	Cluster of differentiation 8 cells
Ces1	Caboxylesterase-1
CHB	Chronic hepatitis B
CI	confidence interval
CKD	Chronic kidney disease
CKF-EPI	Chronic kidney disease epidemiology collaboration
CL/F	Apparent oral clearance after administration of the drug
CL_{Cr}	Creatinine clearance
C_{max}	The maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
COBI / C	Cobicistat
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
PVE	Pharmacovigilance and Epidemiology
DXA	Dual energy x-ray absorptiometry

E2	Estradiol
EC	Ethics committee
EudraCT	European clinical trials database
E/C/F	Elvitegravir/cobicistat/emtricitabine
eGFR	Estimated glomerular filtration rate
EFV	Efavienz
EKG / ECG	Electrocardiogram
ETV	Entecavir
EU	European Union
EVG	Elvitegravir
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
$FEPO_4$	Fractional excretion of Phosphate
FRAX®	Fracture Risk Assessment Tool
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice (Guidelines)
GFR	Glomerular filtration rate
GSI	Gilead Sciences, Inc.
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HbeAb	Hepatitis B e antibody
HbeAg	Hepatitis B e antigen
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HDPE	High-density polyethylene
hERG	Human ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
ITT	Intent-to-treat (analysis or subset)

IRB	Institutional review board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
IUD	Intrauterine device
LdT	Telbivudine
LAM	Lamivudine
LLN	Lower limit of the normal range
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mmHg	Millimeters mercury
NK	Natural killer cells
NOEL	No observed adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Osteocalcin
OCT	Optical coherence tomography
OL	Open-label
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
P-gp	P-glycoprotein
P1NP	Procollagen type 1 amino-terminal propeptide
pol	Polymerase
PK	Pharmacokinetic
PXR	Pregnane X receptor
PT	Preferred Term
PT/INR	Prothrombin time/ International normalized ratio
QD	Once daily (use only in tables)
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
SA	Single agent
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sCr	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure

STR	Single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir Alafenamide, GS-7340
TAF Fumarate	Tenofovir Alafenamide Fumarate, GS-7340-03
TDF	Tenofovir Disoproxil Fumarate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
TLOVR	Time to loss of virologic response
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
TSH	Thyroid stimulating hormone
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

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is a serious global health care problem and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Of the estimated 2 billion people worldwide who have been acutely infected with the hepatitis B virus (HBV), approximately 400 million have developed CHB, and approximately 1 million people die annually from complications of CHB {World Health Organization (WHO) 2000}. Despite the availability of HBV vaccine programs in many countries, new HBV infections are still common even in areas of low endemicity. For example, approximately 80,000 people in the United States (US) become acutely infected each year, according to an estimate from the Centers for Disease Control and Prevention {Centers for Disease Control and Prevention (CDC) 2003}. Following acute HBV infection, approximately 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}.

Chronic hepatitis B has a broad clinical spectrum, ranging from asymptomatic, slowly progressive illness to severe, and more rapidly progressive liver disease. Chronic hepatitis B may remain quiescent for many years and represent a risk factor for progression to cirrhosis, liver failure, and death within a few years. Approximately 25% of subjects with CHB will ultimately develop serious liver disease such as hepatic decompensation, cirrhosis, or HCC {Zuckerman 1996}. The development of nucleos(t)ide analogues has been a major breakthrough for the treatment of CHB, providing effective suppression of viral replication and reducing the risk of long term complications. However, if viral replication resumes as a result of resistance mutation development, the clinical benefit is lost. The rate of resistance development in treatment-naive subjects varies depending on the treatment: up to 70% after 4 years with lamivudine (LAM), up to 29% after 5 years with adefovir dipivoxil (ADV), 25%/11% in hepatitis B e antigen positive/negative (hepatitis B e antigen [HBeAg]+/–) subjects after 2 years with telbivudine (LdT), and 1.2% after 5 years with entecavir (ETV). To date, resistance to TDF has not been documented {Marcellin 2011}.

Tenofovir DF (Viread®) 300 mg once daily was first approved for the treatment of CHB in Turkey on 28 March 2008, and is currently approved in 101 countries, including the US, Canada, and Europe. Approval of TDF for CHB was based primarily on 48 week data from 375 adult subjects with HBeAg CHB and 266 subjects with HBeAg+ CHB who enrolled in the similarly designed pivotal studies GS-US-174-0102 (HBeAg subjects) and GS-US-174-0103 (HBeAg+ subjects). In study GS-US-174-0102, TDF 300 mg once daily was shown to be superior to ADV 10 mg once daily for the treatment of HBeAg–/antibody to hepatitis B e antigen (anti-HBe)-positive (presumed precore mutant) chronic HBV infection. At 48 weeks, 70.8% of subjects in the TDF group (n = 250) had a complete response (plasma HBV deoxyribonucleic acid [DNA] < 69 IU/mL [400 copies/mL] and histologic improvement characterized by ≥ 2 point reduction in the Knodell necroinflammatory score and no worsening of Knodell fibrosis), compared to 48.8% of subjects in the ADV group (n = 125; $p < 0.001$) {Marcellin 2007}. In study GS-US-174-0103 (HBeAg+ subjects), at 48 weeks,

66.5% of subjects in the TDF group (n = 176) had a complete response, compared to 12.2% in the ADV group (n = 90; p < 0.001) {Heathcote 2007}. Subjects in both studies who completed the 48-week double-blind treatment period (including the end-of-blinded-treatment biopsy) were eligible to continue in an open-label (OL) extension phase consisting of treatment with TDF up to Week 480 (Year 10).

In both Phase 3 studies, for viremic subjects originally randomized to ADV who rolled over to open-label TDF at Week 48, HBV DNA values decreased sharply during the first 16 weeks of TDF therapy. At Week 96, the percentages of subjects with plasma HBV DNA < 400 copies/mL were not significantly different between treatment groups in both studies. Viral suppression was maintained through Week 240 of these 2 pivotal studies in those subjects receiving continued treatment with TDF for 240 weeks (TDF–TDF group), and in those subjects who received 192 weeks of TDF treatment following an initial 48 weeks of treatment with ADV (ADV–TDF group). Based on results from a pooled histology analysis at Year 5 for these 2 studies, 96.2% of subjects on open-label TDF experienced either improvement or no change in fibrosis (by Ishak fibrosis scoring). Further, of the 96 subjects with cirrhosis at baseline (Ishak fibrosis score 5-6), 25% experienced no change in Ishak fibrosis score while 73% experienced reversal of cirrhosis by Week 240 with a reduction in Ishak fibrosis score of at least 2 points (missing = excluded [M = E], data after addition of emtricitabine [FTC] included) {Marcellin 2013}. Importantly, viral suppression (HBV DNA < 69 IU/mL or < 400 copies/mL was documented in 330/334 (99%) of subjects with available histology who were maintained on therapy with an available HBV DNA measurement at Week 240. No mutations associated with TDF resistance developed in subjects treated with TDF for up to 5 years in the pivotal studies {Marcellin 2013}. No phenotypic resistance to TDF has been observed among subjects with virologic breakthrough or who developed conserved-site changes in the HBV polymerase (pol)/reverse transcriptase (RT) during TDF treatment for up to 5 years. Continued treatment with TDF for 5 years revealed no new adverse reactions inconsistent with the known safety profile of TDF. Importantly, these results demonstrate that achievement and maintenance of long term viral suppression with TDF translates into a histological benefit (i.e. fibrosis regression) in the majority of subjects.

While liver biopsy provides important information regarding severity of necroinflammatory activity and fibrosis in diseases such as CHB, it is no longer considered routine in clinical practice for ongoing disease monitoring, and the procedure itself is challenging to perform within the context of clinical trials. Additionally, liver biopsy is costly and limited by sampling error as well as patient reluctance to undergo this invasive procedure. With the availability of non-invasive tests, including FibroTest® (also known as FibroSURE in the U.S.) and Fibroscan®, which have been shown to correlate with histology in liver diseases such hepatitis B {Poynard 2005}, hepatitis C {Ngo 2006}, and non-alcoholic fatty liver disease {Poynard 2007}, the need for liver biopsy has been largely replaced, particularly for ongoing monitoring of changes in fibrosis.

Tenofovir DF is also approved worldwide in many markets for administration in combination with other antiretroviral agents for treatment of human immunodeficiency virus (HIV)-1 infection (first approval in 2001). Tenofovir DF is also a component of Truvada® (FTC 200 mg/TDF 300 mg), a marketed fixed-dose combination product for treatment of HIV-1

infection in combination with other antiretroviral agents. More recently, TDF has been included in single tablet regimens (STRs) for treatment of HIV infection. Three STRs are currently approved for once-daily administration in the treatment of HIV-1 infection, efavirenz (EFV)/FTC/TDF (Atripla®), FTC/rilpivirine (RPV)/TDF (Complera®/Eviplera), and more recently, elvitegravir (E)/cobicistat (C)/emtricitabine (F)/TDF (Stribild™). The newly approved Stribild™ STR tablet, which contains a fixed-dose combination of E/C/F/TDF (150/150/200/300 mg), has been approved in the United States by the Food and Drug Administration (FDA) for the treatment of HIV-1 infection in treatment-naïve adults. E/C/F/TDF is the first approved STR that combines an integrase strand transfer inhibitor (elvitegravir) with a nucleoside reverse transcriptase inhibitor (NRTI) backbone into a once-daily tablet. Since Viread® was first marketed on 31 October 2001, the overall exposure to TDF up to 31 May 2013 from branded Viread®, Truvada®, Atripla®, Complera® and Stribild®, combined up to 31 May 2013, is estimated to be in excess of 6 million patient years

TDF is a preferred oral N(t)RTIs for treatment of CHB infection by all current treatment guidelines. For the majority of CHB subjects, life-long treatment is required as only a small percentage (< 10%) of subjects experience sustained loss of hepatitis B surface antigen (HBsAg), and as a consequence, achieve an effective cure of the disease. Though highly effective, long term use of TDF is associated with nephrotoxicity and reduced bone mineral density in some subjects {Panel on Antiretroviral Guidelines for Adults and Adolescents 2012}. Thus, alternative therapies with high antiviral potency, a high genetic barrier to resistance development, and improved long term safety and tolerability are needed in order to further advance treatment of chronic HBV infection worldwide.

Tenofovir alafenamide (TAF), a novel “intracellular” prodrug of tenofovir (TFV), has the potential to advance treatment of chronic HBV infection. In contrast to TDF, an oral prodrug that is rapidly cleaved by esterases in the intestines and plasma to TFV, TAF has been specifically synthesized to be more stable in resisting early enzymatic cleavage following oral administration and remain mostly intact until penetrating target cells. By virtue of this key distinguishing property, TAF when administered at a lower dose than TDF, is capable of efficiently delivering active drug (e.g. tenofovir diphosphate [TFV-DP]) to the cells where it is needed (e.g. HBV-infected hepatocytes, HIV-infected lymphoid cells) while systemic exposures of TFV are greatly reduced in comparison to oral administration of TDF 300 mg. These features are hypothesized to translate into the potential for effective suppression of viral replication and an improved tolerability and safety profile.

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-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is a next generation oral prodrug of TFV, a nucleotide analog that inhibits reverse transcription in HIV-1 and HBV. TFV is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) and HBV pol/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, the form being used in GS-US-292-0102 (Phase 2 study in HIV subjects) and GS-US-320-0101 (Phase 1b study in HBV subjects), is considered comparable to GS-7340-02 based on physical/chemical properties of GS-7340-02, the form that has been used in previous studies and a number of currently ongoing studies. Importantly, both GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

For further information on TAF (GS-7340), please refer to the latest Investigator's Brochure for GS-7340.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Primary Pharmacodynamics

TAF is converted intracellularly by cathepsin A (CatA) and carboxylesterase-1 (Ces1) to form TFV (i.e, a nucleoside monophosphate analog) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, and is subsequently converted to TFV-DP by cellular kinases. The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {Robbins 1995} and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2. Analysis of primary cells showed that CatA activity varied minimally in both human cluster of differentiation 4 (CD4+) T-lymphocytes and macrophages. CatA activity was equivalent in resting and activated CD4s and approximately 2-fold higher in macrophages. Intracellular metabolites of TAF were similar among individual donors in both CD4+ T-cells and macrophages. Carboxylesterease-1 (Ces1) which is highly expressed in liver, contributes to TAF conversion to TFV, particularly in hepatocytes {Bam 2012, Birkus 2012}.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, CD4+ and CD8+ T-cells, NK cells, B-cells and macrophages/monocytes. TAF is metabolized inside host cells to the active metabolite TFV-DP. Concentration of the active metabolite TFV-DP was substantial in all cell populations. Additionally, a 24-hour continuous incubation of TAF in primary human hepatocytes in vitro resulted in approximately 120- or 5-fold higher levels of TFV-DP compared to incubation of TFV or TDF, respectively (AD-120-2017).

1.2.2.2. Safety Pharmacology

TAF monofumarate (GS-7340-02) has been evaluated to determine potential 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). GS-7340-02 (at 1000 mg/kg) reduced distal transit and increased stomach weights starting 2 hours post dosing with reversibility

beginning by 6 hours after dosing. The NOEL for gastrointestinal motility was 100 mg/kg. The IC_{50} for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 μM.

1.2.2.3. Nonclinical Pharmacokinetics

All nonclinical pharmacokinetic experiments in this section were performed using TAF monofumarate (GS-7340-02), and all study data described in this section reflect the dosage of the monofumarate. For reference, 100 mg of GS-7340-02 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 12.5 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 IV studies of TFV. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hrs. 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.

Tenofovir 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.

The hepatic extraction of TAF was estimated to be 70% suggesting that TAF was rapidly cleaved by hepatic hydrolases including Ces1 and CatA {Babusis 2013}. An in vitro study to evaluate effects of inhibitors of CatA or Ces1 on TAF metabolism in primary human hepatocytes is ongoing. Single and repeat dose dog liver pharmacokinetic studies are planned.

1.2.2.4. Nonclinical Toxicology

TAF monofumarate (GS-7340-02) was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9 months and was negative in genetic toxicology studies.

In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment. GS-7340-02 also appeared to increase biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D_3 at doses of 25 mg/kg/day and above. In chronic studies in dogs after 9 months of treatment with GS-7340-02, the primary target organs were kidney and bone.

GS-7340-02 had no discernible electrocardiograph (ECG/EKG) effect at the low dose of 2 mg/kg/day and slightly prolonged PR intervals at 6 and 18/12 mg/kg/day (started at 18 mg/kg/day, then reduced to 12 mg/kg/day at Weeks 7-8). Additionally, at Week 39, GS-7340-02 appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, decreases in serum T3 were noted for animals receiving 18/12 mg/kg/day but was reversible at the 3 month recovery period. Minor hematological and biochemistry parameters changes were observed but remained within normal historical ranges with the following exceptions: AST (~ 100% increase) and total bilirubin (~ 40% increase). There were no clear treatment-related effects observed in monkeys following 28 days of treatment, including no changes in mitochondrial function.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day (tenofovir AUC = 3758 ng•h/mL); the 9-month dog study defined a NOAEL of 2 mg/kg/day (tenofovir AUC = 1180 ng•h/mL), and the 28-day nonhuman primate study defined a NOAEL of 30 mg/kg/day (tenofovir AUC = 5870 ng•h/mL). In conjunction with the nonclinical data with TDF and the clinical experience with TDF and TAF, these toxicology studies support studies in humans of doses up to 150 mg/day (equivalent to 120 mg free base, the highest anticipated human dose) for chronic treatment.

At the time of the rodent toxicity studies, the bioassay could not detect plasma TAF, possibly due to instability in the matrix.

Because of the lack of exposure to the prodrug in mice and rats and achievable TFV exposures less than previously tested in chronic and carcinogenicity studies with TDF, carcinogenicity studies in mice and rats with TAF are currently not required per agreement with FDA and EMA.

Also, TAF does not need to be evaluated in perinatal-postnatal reproductive toxicology studies per agreement with FDA and EMA. Reproductive tissues were examined in repeat-dose toxicology studies in the rat, dog, and monkey. There were no clearly treatment-related histologic alterations or changes in organ weights in the rat and the dog following chronic daily dosing, or in the monkey.

The TAF fumarate (GS-7340-03) oral rat fertility study is ongoing (Report No. TX-120-2012; report in progress).

1.2.3. Clinical Trials of Tenofovir Alafenamide (TAF, GS-7340)

To date, a total of 8 Phase 1 and Phase 1/2, or Phase 2, clinical trials of tenofovir alafenamide (TAF) have been conducted or are ongoing in 528 subjects. This includes seven HIV studies (total of 477 subjects; 2 completed Phase 1/2 studies [68 subjects], 3 completed Phase 1 studies [83 subjects], and 2 ongoing Phase 2 studies [326 subjects]), and 1 Phase 1b HBV study (completed enrollment; 51 subjects). TAF is presently in Phase 3 for treatment of HIV-1 infection in combination with E, C and F, and a Phase 1b study has completed enrollment and dosing for treatment of chronic HBV.

Clinical trials entailing the use of TAF (dose[s] studied) for HIV-1 infection and other Phase 1 studies include:

- GS-120-1101, a Phase 1/2 study of the pharmacokinetics and antiviral activity of TAF (GS-7340 [50 mg and 150 mg]) in HIV infected subjects (completed)
- GS-US-120-0104, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV infected subjects (completed)
- GS-US-120-0107, a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-7340 (25 mg and 150 mg) on the QT/QTc interval in healthy subjects (completed)
- GS-US-120-0108, A Phase 1, Open-Label, Parallel-Design Study to Evaluate the Pharmacokinetics of GS-7340 (25 mg) in Subjects with Severe Renal Impairment (completed)
- GS-US-120-0109, A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism and Excretion of GS-7340 (25 mg [completed])

Further details regarding these studies are provided in the table below (Table 1-1). In Phase 1/2 studies in HIV-infected subjects (Studies 120-1101 and 120-0104), the short-term safety/tolerability, PK, and antiviral activity of TAF when given as a stand alone agent (SA) were evaluated over a range of doses. In Study 120-0104, at TAF doses of 25 mg or higher, near-maximal HIV RNA suppression was observed at Day 10, and importantly, single dose PK assessments of TAF (8 mg, 25 mg, or 40 mg) and TDF (300 mg) demonstrated that the TAF-generated TFV systemic exposures (AUC_{inf}) were markedly lower (approximately 90% lower at TAF 25 mg) than the TFV exposure generated with TDF 300 mg. For HIV Phase 2 (and Phase 3) studies, however, a 10 mg dose of TAF was selected for inclusion as a component of the elvitegravir (E)/ cobicistat (COBI, or "C")/emtricitabine(F)/TAF single tablet regimen (STR) in comparison to the E/C/F/TDF STR control arm. A reduction in dose from 25 mg to 10 mg of TAF in the E/C/F/TAF STR is required based on a drug-drug interaction between TAF and COBI resulting in increased exposures of both TAF and TFV which is likely a consequence of Pgp-mediated inhibition of TAF and TFV efflux within the gut by COBI. Importantly, the resultant TFV exposures when TAF is dosed at 10 mg with COBI in the E/C/F/TAF STR formulation are similar to TFV exposures generated with TAF 25 mg given as a SA. Given that TAF exposures with E/C/F/TAF.

10 mg are comparable to those with TAF given alone, safety results in HIV trials using this formulation are being assessed at a TAF dose that is considered therapeutically equivalent to TAF 25 mg. Thus, HIV studies conducted at TAF exposures similar to those expected in HBV provide the basis for supporting safety data for the TAF HBV development program.

Table 1-1. Summary of TAF Phase 1 and Phase 1/2 Studies for HIV Infection

Study #	Population	Design	Dosing/Duration	Rationale
HIV Studies (Phase 1/2)				
120-1101	N = 30 Treatment naïve	Dose escalation 3 treatment cohorts	TAF 50 mg, 150 mg, TDF 300 mg; multiple dosing for 14 days	Short-term proof of concept study; safety, PK, and antiviral efficacy
120-0104	N = 38 Treatment naïve (no ARV within 90 days of screening)	Randomized (2:2:2:1:2) partially blinded	TAF 8 mg, 25 mg, 40 mg, TDF 300 mg, or placebo (PBO) for 10 days; off treatment follow up to Day 21	Confirmatory study for Study 1101 using a TAF reformulation; more rigorous design, evaluate lower TAF doses
Ongoing Supportive Phase 1 Studies				
120-0107	N = 48 Males/females, age 18-45	Thorough QT (TQT)	TAF 25 mg, 125 mg; each subject dosed 3 times for 37 days (with 10 day wash-out period)	Regulatory requirement
120-0108	N = 27 (14 with severe renal impairment [CrCL 15-29 mL/min] and 13 matched controls [CrCL ≥ 90 mL/min])	PK in Renal impairment	TAF 25 mg single dose with 14 days of follow up	Characterizing TAF and TFV PK in severe renal impairment (to demonstrate no need for TAF dose adjustment)
120-0109	N = 8 healthy volunteer, male subjects	Mass Balance	Single radio-labeled TAF 25 mg dose with 21 days of follow up	Regulatory requirement

Clinical trials entailing the use of TAF for the treatment of CHB virus:

- GS-US-320-0101 A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics and Anti-HBV Activity of GS-7340 in Treatment-Naïve Adults with Chronic Hepatitis B (CHB) Infection (enrollment and dosing completed)

The two proof-of concept studies, GS-120-1101 and GS-US-120-0104, as well as GS-US-292-0101, a STR bioequivalence study, were performed using TAF monofumarate (GS-7340-02). All subsequent studies discussed herein were performed using TAF fumarate (GS-7340-03).

GS-120-1101 was a Phase 1/2 randomized double-blind, active-controlled, dose escalation study of the safety, tolerance, pharmacokinetics, and antiviral activity of TAF in antiretroviral-naïve subjects who are chronically infected with HIV-1. The subjects were randomized to receive

14 days of monotherapy, fasting, with GS-7340-02 50 mg (40 mg GS-7340 [free base] equivalent) QD, 150 mg (120 mg GS-7340 [free base] equivalent) QD, or tenofovir DF 300 mg QD (n = 10 per group). TAF was rapidly absorbed into the systemic circulation, and subsequently following attainment of C_{max}, was eliminated rapidly with a short plasma half-life (20-40 minutes). Compared with TDF, GS-7340-02 50 mg provided a ~16-fold lower TFV C_{max} (207 ng/mL vs 13 ng/mL), about 2-fold longer elimination half-life (26 hours vs 48 hours) and lower overall systemic tenofovir exposure (AUC_{inf}: 1814 ng.h/mL vs 383 ng.h/ml). TAF monofumarate 150 mg provided lower C_{max} (42 ng/mL), but comparable AUC_{inf}: (1740 ng.h/mL) as TDF. In PBMCs, TFV was detected earlier, more frequently, and in higher concentrations following dosing of TAF monofumarate as compared to TDF. The intracellular delivery of TFV is approximately 30-fold greater for GS-7340-02 versus TDF. The decrease from Baseline to Day 14 in plasma HIV-RNA levels was greater for groups treated with GS-7340-02 50 mg ($p = 0.02757$) or 150 mg ($p = 0.0010$) than the group that received TDF 300 mg. The median changes from baseline in plasma HIV-1 RNA after 14 days of monotherapy were
0.96 $\log_{10}$ copies/mL for TDF 300 mg, 1.65 $\log_{10}$ copies/mL for GS-7340-02 50 mg, and
1.68 for GS-7340-02 150 mg.

A second proof-of-concept study, GS-US-120-0104, evaluated monotherapy, fasting, with three lower doses of TAF compared with TDF 300 mg, or placebo, administered for 10 days. Potent antiviral activity was achieved with TAF in treatment-naïve HIV-1 infected subjects; mean viral load declines for both the 25 mg and 40 mg doses were statistically better than the 8 mg dose. TAF exposure (AUC) was best associated with antiviral activity despite its short plasma half-life (~ 30 min). TFV AUC values were 97%, 87%, and 80% lower at 8 mg, 25 mg, and 40 mg TAF respectively, compared to TDF administration. When compared to 40 mg and historical 120 mg data, 25 mg TAF provides near maximal anti-HIV-1 activity. From this PK-PD analysis, a target exposure of a dose of 25 mg TAF monotherapy is expected to provide near maximal antiviral activity and ~ 90% reduction in circulating TFV.

Study GS-US-120-0107 is a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of TAF on the QT/QTc interval in healthy subjects. This was a negative thorough-QTc study. No effect of TAF was observed on the QTcF interval (ie, no QTc interval prolongation > 10 msec at any time point post-dose and assay sensitivity was confirmed via the positive control [moxifloxacin]). As such, these findings satisfy the guidelines set forth in the International Conference on Harmonization (ICH) E14 guidance and support the conclusion that there is no significant effect of TAF on the QT/QTc interval.

Study GS-US-120-0108 is a Phase 1, open-label, parallel-design study to evaluate the PK of TAF in subjects with severe renal impairment. TAF was well tolerated in the study. Subjects with severe renal impairment had < 2-fold higher TAF and 5-6 fold higher TFV systemic exposures as assessed by AUC relative to subjects with normal renal function. TFV exposures in subjects with severe renal impairment are comparable to those with normal renal function receiving 300 mg TDF QD. Given the extensive safety data available for TDF at a dose of 300 mg, TFV exposures in severely renally impaired subjects similar to those associated with TDF 300 mg are deemed appropriate for further study of TAF in HIV-infected subjects without TAF dose modification.

Preliminary results from Study GS-US-120-0109, a Phase 1 PK, metabolism and excretion study demonstrated that TAF is eliminated in both feces and urine. TAF and its metabolites are eliminated in both feces and urine. The predominant species detected in feces and urine is TFV, accounting for 31.4% ± 10.4% and 22.2% ± 4.47% respectively of the total radioactive dose. These human data are consistent with the established preclinical profile of TAF. Following administration of TAF, plasma [^{14}C] radioactivity showed a time dependent profile with TAF as the most abundant species in the initial few hours and uric acid, a byproduct of TAF metabolism, in the remaining period. The whole blood-to-plasma concentration ratio of [^{14}C] radioactivity increased from 0.511 at 0.25 hours post dose to 2.32 at 216 hours post dose, suggesting a relatively slower clearance of [^{14}C] radioactivity from blood cells relative to the plasma [^{14}C] radioactivity time-course. In addition to TFV and uric acid, additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and therefore should not cause any safety risk. TAF 25 mg tablets administered together with tracer dose of [^{14}C] radiolabeled TAF as a single oral tablet, were well tolerated.

HBV Study – GS-US-320-0101

In HBV subjects, a 28 day Phase 1b study (GS-US-320-0101), was conducted to evaluate safety/tolerability, pharmacokinetics, and antiviral activity of TAF at doses of 8 mg, 25 mg, 40 mg, and 120 mg compared to TDF 300 mg control in 50 subjects (10/cohort). As of April 2, 2013, enrollment was completed (n = 51) and all subjects have completed study drug dosing through Day 29.

Preliminary data suggest that all treatment groups were generally well matched (Table 1-2) and representative of the chronic HBV population. Overall, the majority of subjects were male (66.7%), and of Asian descent (56.9%). Of the 51 randomized subjects, 27 (53%) and 24 (47%) were HBeAg-negative and HBeAg-positive, respectively. Median age ranged among groups from 34 years in the 8 mg and 25 mg TAF groups to 40 and 42 years in the 40 mg and 120 mg TAF groups, respectively; median age in the TDF group was 34 years. The most common HBV genotype at enrollment was genotype C (16/51; 31%), the proportions of other genotypes were: A (7/51; 14%), B (10/51; 20%), D (9/51; 18%), and E (9/51; 18%). The distribution of HBV genotypes was similar within groups, with the exception of a higher proportion (5 of 11 [45.5%]) of subjects in the 40 mg TAF group having genotype B.

Table 1-2. GS-US-320-0101: Baseline Demographics and Disease Characteristics

	TAF 8 mg (N = 10)	TAF 25 mg (N = 10)	TAF 40 mg (n = 11)	TAF 120 mg (N = 10)	TDF 300 mg (N = 10)
Male sex, n (%)	4 (40%)	8 (80%)	8 (73%)	8 (80%)	6 (60%)
Median (range) age, yr	34 (19 – 57)	34 (23 – 42)	40 (19 – 60)	42 (25 – 51)	34 (25 – 49)
Race, n (%)					
Asian	CCI	CCI	[redacted]	[redacted]	[redacted]
Black or African American	CCI	[redacted]	[redacted]	[redacted]	[redacted]
White	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range) BMI, kg/m^2	26.6 (17.9 - 32.3)	25.9 (20.2 – 46.0)	24.1 (21.0 – 31.8)	24.5 (19.8 – 34.0)	25.6 (19.6 – 31.8)
Median (range) body weight, kg	69.7 (49.9 – 94.0)	74.7 (61.0 – 134.4)	62.5 (56.0 – 104.1)	71.2 (54.0 – 110.0)	78.3 (47.2 – 98.8)
Median (range) CL_{Cr}, mL/min	107.1 (88.8 - 158.0)	121.7 (84.8 - 239.1)	117.9 (75.6 - 153.8)	107.6 (81.3 - 143.5)	127.1 (64.2 - 196.4)
Median (range) HBV DNA, $\log_{10}$ IU/mL	6.26 (3.73 – 8.98)	6.35 (3.56 – 8.93)	5.37 (3.27 – 8.57)	5.98 (3.71 – 9.74)	4.78 (3.97 – 8.85)
Median (range) HBsAg, $\log_{10}$ IU/mL	4.10 (1.55 – 4.72)	3.59 (1.47 – 4.72)	3.64 (1.67 – 4.72)	3.84 (2.64 – 4.72)	3.93 (2.95 – 4.72)
Median (range) ALT, U/L	41.0 (23 - 83)	52.5 (33 - 106)	50.0 (11 - 169)	43.0 (26 - 114)	27.5 (11 - 107)
HBeAg-negative, n (%)	5 (50%)	4 (40%)	8 (73%)	5 (50%)	5 (50%)
HBV genotype, n (%)					
A	1 (10%)	1 (10%)	1 (9%)	1 (10%)	3 (30%)
B	1 (10%)	2 (20%)	5 (45%)	1 (10%)	1 (10%)
C	2 (20%)	4 (40%)	3 (27%)	3 (30%)	4 (40%)
D	3 (30%)	2 (20%)	1 (9%)	3 (30%)	0
E	3 (30%)	1 (10%)	1 (9%)	2 (20%)	2 (20%)

Preliminary safety results are summarized in the table (Table 1-3) below. Overall, TAF was safe and well tolerated in HBV subjects. No subjects experienced a serious adverse event (SAE), or Grade 3 or 4 treatment emergent adverse event, and no subjects required treatment discontinuation for an AE. Treatment emergent AEs were generally mild to moderate, and included gastrointestinal complaints (nausea, vomiting, diarrhea, epigastric discomfort), fatigue, lethargy, headache, and dizziness. Grade 3 laboratory abnormalities were seen in 3 subjects in

the TAF 40 mg group (1 subject each with creatine kinase elevation, glycosuria, and hematuria), 2 subjects in the TAF 120 mg group (1 subject each with elevated transaminases [both AST and ALT occurring during treatment follow-up], and amylase elevation), and in 1 subject in the TDF arm (amylase elevation). The subject with Grade 3 glycosuria in the TAF 40 mg group, experienced this abnormality at Day 29 which was associated with a corresponding serum glucose elevation (212 mg/dL); the subject also had a history of diabetes mellitus.

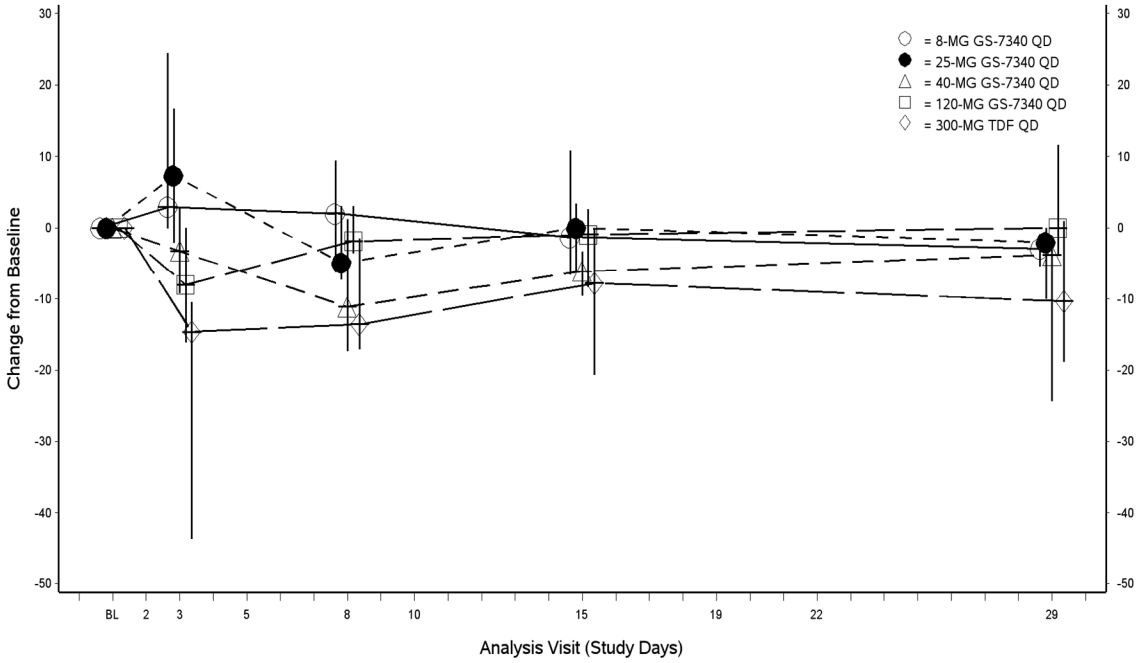
Table 1-3. GS-US-320-0101: Treatment-Emergent Adverse Events and Laboratory Abnormalities: Overall Summary, Safety Analysis Set

	TAF 8 mg (N = 10)	TAF 25 mg (N = 10)	TAF 40 mg (n = 11)	TAF 120 mg (N = 10)	TDF 300 mg (N = 10)
Subjects Experiencing Any Treatment-Emergent Adverse Event	7 (70%)	6 (60%)	6 (55%)	8 (80%)	5 (50%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	2 (20%)	4 (40%)	3 (27%)	4 (40%)	5 (50%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event	1 (10%)	1 (10%)	0	4 (40%)	2 (20%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	0	0	0	3 (30%)	1 (10%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	0	0	0	0	0
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Laboratory Abnormality	0	0	3 (27%)	2 (20%)	1 (10%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	0	0	0	0	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	0	0	0	0	0

Given the significantly smaller declines in creatinine clearance (CL_{Cr}) observed at Week 24 with TAF relative to TDF in the HIV Phase 2 study (GS-US-209-0102; Section 1.2.4), changes in CL_{Cr} were also assessed in HBV subjects participating in GS-US-320-0101. After 4 weeks of dosing, numerically smaller changes in CL_{Cr} at Day 29 were seen in HBV subjects receiving TAF compared with TDF (Figure 1-1). At Day 29, median (range) change from baseline in CL_{Cr} was 2.0 (13.2, 9.6) mL/min for the TAF 25 mg group compared with a change of 10.4 (35.7, 13.0) mL/min in the TDF group. Further, there were no notable differences in CL_{Cr}

change among the two lowest dose groups (TAF 8 mg and TAF 25 mg), and the highest dose group (120 mg). An early decline in CL_{Cr}, similar to that observed in the TDF group was noted in the TAF 40 mg group; however, by Day 29 the change in CL_{Cr} was similar to the other TAF groups. These results are consistent with findings in HIV subjects receiving the E/C/F/TAF 10 mg STR and provide additional evidence to support the concept that lower TFV exposures with TAF relative to TFV exposures with TDF are associated with notable differences in renal function as determined by estimated CL_{Cr}.

Figure 1-1. Median Change (Q1, Q3) from Baseline in Creatinine Clearance (Cockcroft-Gault Method) in GS-US-320-0101



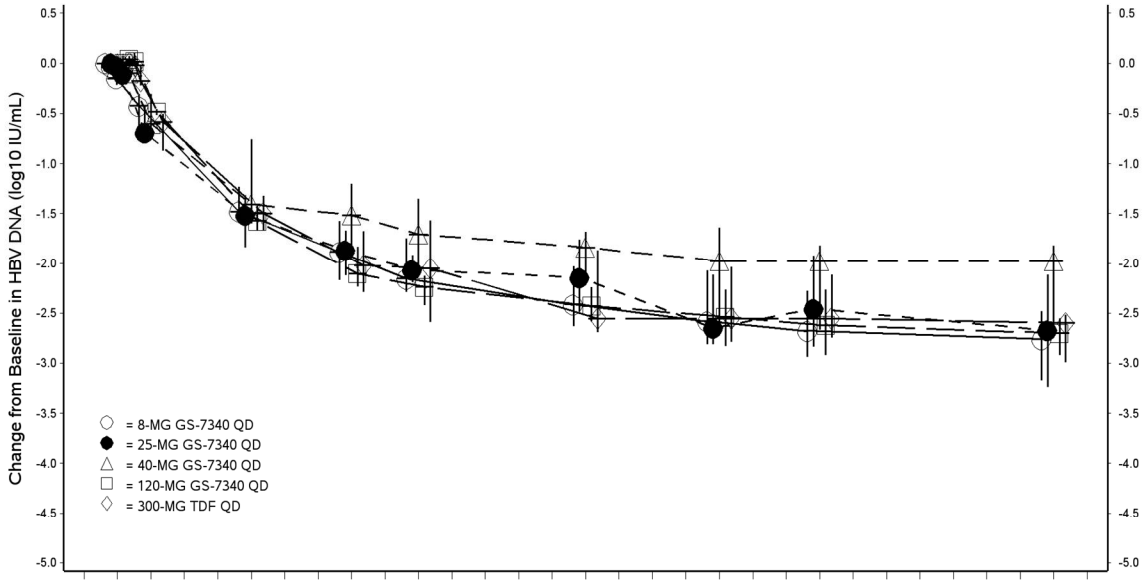
8-MG GS-7340 QD:	10	3	10	10	10
25-MG GS-7340 QD:	10	2	9	10	10
40-MG GS-7340 QD:	11	2	11	9	11
120-MG GS-7340 QD:	10	2	9	10	9
300-MG TDF QD:	10	3	10	10	10

Baseline is defined as Day 1.

Over 28 days of study drug treatment, similar median declines in HBV DNA levels were observed among treatment groups (Figure 1-2). Overall, viral decay results among subjects who received treatment with TAF demonstrated the absence of a dose effect. In addition, the HBV DNA declines with TAF (n = 41) over 28 days of dosing were similar to HBV DNA declines observed in the TDF 300 mg group (n = 10). A summary of change from baseline in HBV DNA results at Day 15 and Day 29 is provided in the table below (Table 1-4) below. Among TAF groups, median change from baseline in HBV DNA at Day 29 ranged from 1.98 log_{10} IU/mL for the TAF 40 mg group to 2.76 log_{10} IU/mL for the TAF 8 mg group. For TAF 25 mg, the change from baseline in HBV DNA at Day 29 was 2.67 log_{10} IU/mL. Consistently smaller declines in HBV DNA over time, and slightly lower median change from baseline in HBV DNA

were observed in the TAF 40 mg group at Day 29. The reason for this is unclear and possibly related to a lower median HBV DNA value at Baseline (Table 1-4). In this group, 5/11 (45.5%) subjects had a baseline HBV DNA value below 5.0 $\log_{10}$ IU/mL. In comparison to TAF groups, the change from baseline in HBV DNA at Day 29 was 2.60 $\log_{10}$ IU/mL with TDF 300 mg.

Figure 1-2. GS-US-320-0101: Median Change (Q1, Q3) from Baseline in HBV DNA (Log_{10} IU/mL) by Treatment Group



8-MG GS-7340 QD:	10	10	10	9	10	10	10	10	10
25-MG GS-7340 QD:	10	10	10	10	10	10	9	10	10
40-MG GS-7340 QD:	11	11	10	11	11	9	11	11	9
120-MG GS-7340 QD:	10	9	10	9	10	10	9	10	9
300-MG TDF QD:	10	9	9	10	10	10	10	10	10

Baseline is defined as Day 1/pre-dose.

Table 1-4. GS-US-320-0101: HBV DNA Results: Median Change from Baseline at Day 15 and Day 29 by Treatment Group

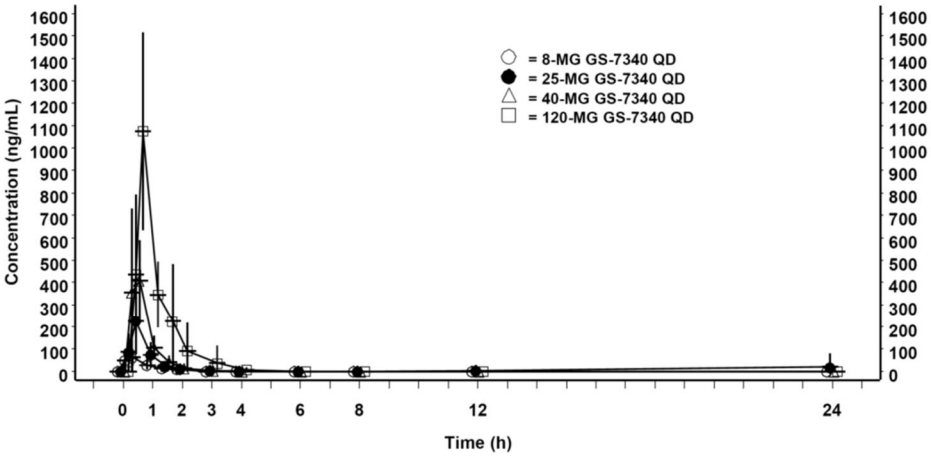
	TAF 8 mg (N = 10)	TAF 25 mg (N = 10)	TAF 40 mg (n = 11)	TAF 120 mg (N = 10)	TDF (N = 10)
HBV DNA (Log_{10} IU/mL) at Baseline (Day 1), Median (Q1, Q3), [Min, Max]	6.26 (5.01, 8.50) CCI	6.35 (4.10, 7.68) CCI	5.37 (3.42, 7.78) [3.27, 8.57]	5.98 (4.34, 8.83) CCI	4.78 (4.11, 6.86) CCI
n =	10	10	9	10	10
Change from Baseline in HBV DNA (Log_{10} IU/mL) at Day 15, Median (Q1, Q3), [Min, Max]	-2.41 (-2.63, -2.03) CCI	-2.14 (-2.48, -1.76) CCI	-1.84 (-2.18, -1.68) [-2.81, -0.98]	-2.43 (-2.58, -2.25) CCI	-2.55 (-2.69, -1.87) CCI
n =	10	10	9	9	10
Change from Baseline in HBV DNA (Log_{10} IU/mL) at Day 29, Median (Q1, Q3), [Min, Max]	-2.76 (-3.17, -2.48) CCI	-2.67 (-3.23, -2.12) CCI	-1.98 (-2.65, -1.82) [-3.11, -1.67]	-2.70 (-2.92, -2.56) CCI	-2.60 (-2.99, -2.52) CCI

Plasma concentration-time profiles were generated after intensive pharmacokinetic sampling following a single dose on Day 1 for subjects who were randomized to receive TAF 8, 25, 40, or 120 mg, or TDF 300 mg (N=51). The respective plasma concentration-versus-time profiles are shown in Figure 1-3 and Figure 1-4 (TFV). Pharmacokinetic parameters were calculated via non-compartmental analysis.

TAF Pharmacokinetic Results

In general, the concentration-time profiles for TAF over the range of doses studied in CHB subjects were consistent with previous results in the healthy volunteers and HIV subjects receiving TAF either as a single agent or as a component of the E/C/F/TAF STR.

Figure 1-3. GS-US-320-0101: Mean (SD) Plasma Concentrations vs. Time on Day 1: TAF (GS-7340), Linear Scale



8-MG GS-7340 QD (n=):	10	10	10	10	10	10	10	3	10
25-MG GS-7340 QD (n=):	10	9	10	10	10	10	9	3	10
40-MG GS-7340 QD (n=):	11	11	11	11	11	11	11	2	10
120-MG GS-7340 QD (n=):	10	10	10	10	10	10	10	3	9

Note: Plasma concentration below limit of quantitation was treated as 0 for summary purpose and was treated as missing for log-transformed data.

Data Extracted: CRF data: 25APR2013
Source: ...\draft2\prog\t-pkconc.sas v9.2 Output file: g-pconc1-mn.out 01MAY2013:16:12

TAF plasma pharmacokinetic parameters are summarized in Table 1-5. Day 1 pharmacokinetic results in CHB subjects participating in GS-US-320-0101 are consistent with previously reported results in the HIV Phase 1/2 study GS-US-120-0104, which evaluated TAF single-dose pharmacokinetics following doses of 8 mg (n=9), 25 mg (n=8), and 40 mg (n=8), versus TDF 300 mg (n=6). In GS-US-120-0104, mean (%CV) $AUC_{0\text{-last}}$ was 38.4 (80.6) ng·h/mL, 139.7 (57.8) ng·h/mL, and 322.1 (42.0) ng·h/mL after single doses of TAF 8 mg, 25 mg, and 40 mg, respectively. Other parameters assessed on Day 1 (C_{max}, T_{max}, and $t_{1/2}$) in GS-US-320-0101 were similar to the results generated in GS-US-120-0104.

Similar findings to the present study were also observed when TAF pharmacokinetic parameters were assessed after multiple doses at steady-state in the ongoing Phase 2 study, GS-US-292-0102, which compares STRs of E/C/F/TAF 10 mg to E/C/F/TDF 300 mg in HIV-1 infected, treatment-naive subjects. Mean (%CV) AUC_{last}, and C_{max} values for TAF at the 10 mg dose in combination with COBI were 230.4 (47.3) ng·h/mL and 232.8 (64.6) ng/mL, respectively. As TAF exposures at the 10 mg dose, when included as a component of the E/C/F/TAF STR, have been shown to be comparable to those with TAF 25 mg given as the stand-alone agent, these results indicate similar TAF exposures in both subjects infected with HIV and those infected with HBV.

Table 1-5. GS-US-320-0101: Single Dose Pharmacokinetic Results for TAF on Day 1

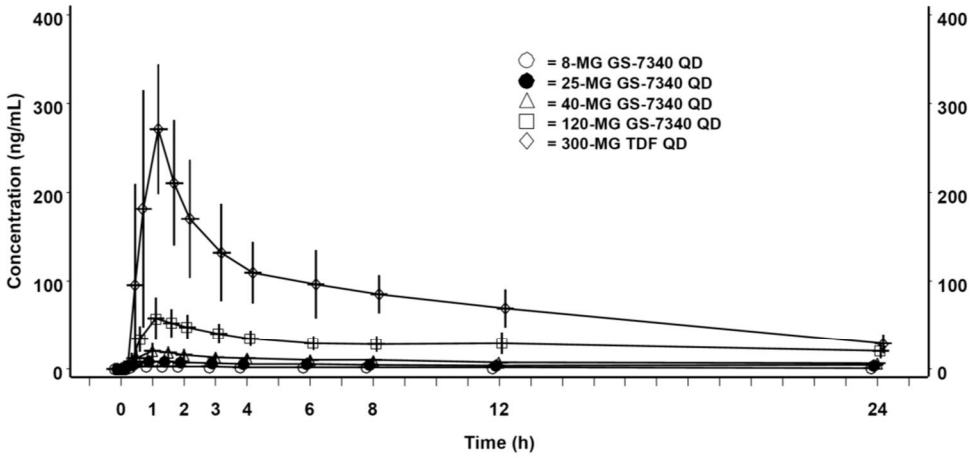
TAF PK Parameter	TAF 8 mg (N = 10)	TAF 25 mg (N = 10)	TAF 40 mg (N = 11)	TAF 120 mg (N = 10)
$AUC_{0\text{-last}}$ (ng·h/mL)	59.2 (54.1)	153.0 (41.1)	328.1 (58.4)	832.4 (39.1)
AUC_{inf} (ng·h/mL)	60.6 (52.8)	154.4 (41.0)	329.8 (58.1)	834.6 (38.9)
C_{max} (ng/mL))	83.2 (46.3)	249.5 (45.9)	527.4 (50.6)	1128.7 (33.7)
T_{max} (h) median	0.5	0.5	0.5	0.5
$T_{1/2}$ (h)	0.36 (23.8)	0.51 (32.6)	0.59 (30.7)	0.76 (30.8)

All results expressed as mean (%CV) unless otherwise stated

TFV Pharmacokinetic Results

Mean (SD) plasma concentration versus time profiles for TFV following single dose administration of ascending doses of TAF and TDF 300 mg are shown in Figure 1-4. At each TAF dose evaluated, plasma TFV concentrations resulting from TAF administration were lower than plasma TFV concentrations following TDF administration. The TFV concentrations achieved from all TAF dose levels in HBV subjects in GS-US-320-0101 are comparable to TFV concentrations achieved after TAF administration in the HIV program.

Figure 1-4. GS-US-320-0101: Mean (SD) Plasma Concentrations vs. Time on Day 1: Tenofovir, Linear Scale



8-MG GS-7340 QD (n=):	10	10	10	10	10	10	10	3	10
25-MG GS-7340 QD (n=):	10	9	10	10	10	10	9	3	10
40-MG GS-7340 QD (n=):	11	11	11	11	11	11	11	2	11
120-MG GS-7340 QD (n=):	10	10	10	10	10	10	10	3	9
300-MG TDF QD (n=):	9	9	10	10	10	10	10	3	8

Note: Plasma concentration below limit of quantitation was treated as 0 for summary purpose and was treated as missing for log-transformed data.

Data Extracted: CRF data: 25APR2013
Source: ...\draft2\prog\t-pkconc.sas v9.2 Output file: g-pconc2-mn.out 01MAY2013:16:12

Tenofovir (TFV) plasma pharmacokinetic parameters are summarized in Table 1-6. As with TAF, Day 1 TFV pharmacokinetic results in CHB subjects participating in GS-US-320-0101 are consistent with those previously reported in the HIV Phase 1/2 study GS-US-120-0104, which evaluated TAF single-dose pharmacokinetics following doses of 8 mg (n=9), 25 mg (n=8), and 40 mg (n=8), versus TDF 300 mg (n=6). In GS-US-120-0104, mean (%CV) AUC_{inf} for TFV were 49.4 (30.3) ng·h/mL, 195.9 (27.2) ng·h/mL, and 287.3 (33.7) ng·h/mL after single doses of TAF 8 mg, 25 mg, and 40 mg, respectively. Mean (%CV) AUC_{inf} for TFV following TDF 300 mg was 1719.2 ng·h/mL. Other parameters assessed on Day 1 (C_{max}, T_{max}, and $t_{1/2}$) in GS-US-320-0101 were similar to results seen in HIV subjects in GS-US-120-0104. As stated earlier, When TAF is included as a component of the E/C/F/TAF STR, a reduced dose (10 mg) is required due to a drug-drug interaction (inhibition of P-gp in the gut by cobicistat) that results in increased exposures of both TAF and TFV (see Section 1.2.4).

Table 1-6. GS-US-320-0101: Single Dose Pharmacokinetic Results for TFV on Day 1

TFV PK Parameter	TAF 8 mg (n=10)	TAF 25 mg (n=10)	TAF 40 mg (n=11)	TAF 120 mg (n=10)	TDF 300 mg (n=10)
$AUC_{0\text{-last}}$ (ng·h/mL)	32.9 (35.0)	90.6 (25.8)	213.4 (40.2)	607.7 (35.4)	1682.1 (28.0)
AUC_{inf} (ng·h/mL),	74.0 (41.2)	171.4 (29.9)	444.6 (43.0)	1572.0 (47.2)	2309.8 (27.9)
Reduction in AUC_{inf}, TAF/TDF (%)	97	93	81	32	N/A
C_{max} (ng/mL),	3.0 (34.5)	8.3 (41.6)	20.3 (43.2)	61.0 (33.5)	306.8 (24.5)
Reduction in C_{max}, TAF/TDF (%)	99	97	93	80	N/A
T_{max} (h) median	1.25	1.0	1.0	1.0	1.0
$t_{1/2}$ (h)	26.7 (23.4)	20.7 (39.6)	26.3 (33.8)	31.4 (38.6)	10.8 (17.4)

The following Section (1.2.4) provides a summary of experience with TAF in HIV-1 infection, including the final Week 24 analysis results for TAF when used as a component of the E/C/F/TAF STR in the HIV Phase 2 study GS-US-292-0102. Because TAF exposures in this ongoing trial are similar to those expected in the TAF HBV development program, these results provide important supporting safety data.

1.2.4. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF)

Phase 1 and 2 clinical trials using TAF, coformulated into the E/C/F/TAF STR for the treatment of HIV-1 infection include:

- GS-US-292-0101, a Phase 1 healthy volunteer study evaluating the relative bioavailability of EVG, FTC, TFV, and COBI when administered as E/C/F/TAF STR relative to E/C/F/TDF or TAF (completed)

- GS-US-292-0103, a Phase 1 healthy volunteer study to evaluate the pharmacokinetics and relative bioavailability of the E/C/F/TAF STR relative to the individual components at GS-7340 doses of 10 mg (STR) or 25 mg SA (completed)

- GS-US-292-0102, a Phase 2 randomized, double-blinded study of the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF STR in HIV-1 infected, antiretroviral treatment-naive adults (ongoing)

1.2.4.1. Summary of Phase 1 Studies (Study GS-US-292-0102, GS-US-292-0103)

Study GS-US-292-0101 is a completed Phase 1 study of 40 subjects evaluating the relative bioavailability of two different formulations of E/C/F/TAF STR, each with TAF dose of 25 mg or 40 mg, versus E/C/F/TDF STR or TAF 25 mg alone. Exposures of EVG, COBI, and FTC were comparable between E/C/F/TAF vs E/C/F/TDF regardless of formulation (monolayer or bi-layer). In contrast, TAF exposures were ~2.2-fold higher (and corresponding tenofovir exposures ~ 3-fold higher) when administered as E/C/F/TAF (25 mg) vs TAF SA 25 mg for both formulations of the E/C/F/TAF. This is likely mediated by inhibition of Pgp-mediated intestinal secretion of TAF by COBI and consistent with data from Study GS-US-311-0101 described below.

Study GS-US-292-0103 is a completed Phase 1 healthy volunteer study which evaluated the PK and relative bioavailability of the E/C/F/TAF STR relative to the individual components at TAF doses of 10 mg (as STR) or 25 mg SA. Results indicate that when dosed as the E/C/F/TAF 10 mg STR, TAF and TFV exposures were comparable to those observed with TAF 25 mg dosed alone. Exposures of EVG, COBI, and FTC were also comparable between the STR and individually dosed formulations.

1.2.4.2. Week 24 Summary of Phase 2 Study (Study GS-US-292-0102)

GS-US-292-0102 is an ongoing Phase 2, randomized, double-blind, multicenter, active-controlled study to assess the safety and efficacy of E/C/F/TAF STR versus E/C/F/TDF in HIV-1 infected, antiretroviral treatment-naive adults with plasma HIV-1 RNA levels ≥ 5,000 copies/mL at Screening.

Eligible subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment arms and randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at Screening:

- Treatment Arm 1: STR of EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (E/C/F/TAF) + placebo-to-match STR of EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg (E/C/F/TDF) once daily (n = 100)

- Treatment Arm 2: STR of EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg (E/C/F/TDF) + placebo-to-match STR EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (E/C/F/TAF) once daily (n = 50)

The Independent Data Monitoring Committee (IDMC) reviewed the safety and study conduct at Week 12 and determined that no changes were required for study GS-US-292-0102. Interim data at Week 24 is presented below.

1.2.4.3. Week 24 Subject Disposition and Demographics

A total of 170 subjects were randomized and treated in this study: 112 subjects in the E/C/F/TAF group and 58 subjects in the E/C/F/TDF group. The full analysis set (FAS) and safety analysis set (SAS) each included all randomized and treated subjects from each group. A total of 24 subjects were included in the pharmacokinetic substudy analysis set. At the time of the Week 24 data analysis, 6 subjects (2.4%) had been discontinued from treatment and 4 subjects (2.4%) had been discontinued from study.

Of the 170 subjects in the FAS and SAS, 165 (97.1%) were male; 115 (67.6%) were white and 50 (29.49%) were black; and the mean age was 36 years (range: 18 to 71 years). Demographic and baseline disease characteristics were similar between the 2 treatment groups.

1.2.4.4. Week 24 Efficacy Results

Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 24

The proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 24 was 86.6% in the E/C/F/TAF group and 89.7% in the E/C/F/TDF group, with a stratum-adjusted difference in the response rate between the 2 treatment groups of 4.9% (95% CI: 15.7% to 5.9%; p = 0.36). Results of the secondary efficacy endpoint confirmed those of the primary analysis. The proportion of subjects with suppression of plasma HIV-1 RNA < 50 copies/mL at Week 24 (time-to-loss of virologic-response [TLOVR] analysis) was 88.4% (99/112) in the E/C/F/TAF group and 84.5% (49/58) in the E/C/F/TDF group. The stratum-adjusted difference in the response rate between the 2 treatment groups was 0.1% (95% CI: 10.4% to 10.2%; p = 0.99). The mean increase in CD4 cell count from baseline to Week 24 was 163 cells/μL in the E/C/F/TAF group and 177 cells/μL in the E/C/F/TDF group (-6 difference in LSM, 95% CI 44 to 33).

1.2.4.5. Week 24 Pharmacokinetic Results

Results from the intensive CCI [redacted] demonstrated that, consistent with data in healthy subjects and HIV-infected subjects treated with TAF monotherapy, E/C/F/TAF (10 mg) produced substantially lower tenofovir systemic exposures than E/C/F/TDF (TDF 300 mg). TAF exhibited a short median (min-max) plasma half-life of 0.47 (0.37 to 0.87) hours with no detectable drug after 8 hours post-administration. Steady-state mean (CV%) AUC_{tau} was 230 ng•hr/mL (47%). PK results for the other components EVG, COBI and FTC were similar to historical data for these agents when administered as E/C/F/TDF (data not shown). In addition, TFV-DP concentrations in peripheral blood mononuclear cells (PBMCs) in subjects in the E/C/F/TAF group showed that TFV-DP was detectable within PBMCs at greater exposures (approximately 5-fold) after administration of E/C/F/TAF than with E/C/F/TDF.

1.2.4.6. Week 24 Safety Results

1.2.4.6.1. Overall Safety

At the time of the 24-week interim analysis, 112 subjects had been treated with E/C/F/TAF for a median duration of 21.1 weeks and 58 subjects had been treated with E/C/F/TDF for a median duration of 21.3 weeks. The overall subject incidence of treatment-emergent adverse events (AEs) was balanced between treatment groups (81.3% E/C/F/TAF, 81.0% E/C/F/TDF) (Table 1-7). The most frequent treatment-emergent AEs (> 10% in either treatment group) were (17.9% E/C/F/TAF, 12.1% E/C/F/TDF) nausea, diarrhea (11.6% E/C/F/TAF, 12.1% E/C/F/TDF), fatigue (11.6% E/C/F/TAF, 8.6% E/C/F/TDF), upper respiratory tract infection (7.1% E/C/F/TAF, 12.1% E/C/F/TDF), and headache (9.8% E/C/F/TAF, 10.3% E/C/F/TDF), respectively.

Most treatment-emergent AEs were assessed as Grade 1 or Grade 2 in severity. The incidence of Grade 3 or 4 AEs was higher in the E/C/F/TAF group (7.1%) compared to the E/C/F/TDF group (3.4%). No Grade 3 or 4 event occurred in > 1 subject; the system organ class (SOC) with the highest subject incidence of Grade 3 or 4 events was Nervous System Disorders (2.7% E/C/F/TAF, 0% E/C/F/TDF). The only Grade 3 or 4 event that was considered by the investigator to be related to investigational product was Grade 3 diarrhea in 1 subject (0.9%) in the E/C/F/TAF group; there were no treatment-related Grade 3 or 4 AEs in the E/C/F/TDF group. Based on these data, there do not appear to be any signature, higher grade AEs associated with the use of E/C/F/TAF through 24 weeks of treatment.

More subjects in the E/C/F/TAF group compared to the E/C/F/TDF group also had treatment-emergent serious AEs (SAEs) (5.4% vs 3.4%) or AEs leading to premature treatment discontinuation (3.6% vs 0). None of these events occurred in > 1 subject, and none of the SAEs were considered by the investigator to be related to treatment with investigational product. The system organ class (SOC) with the highest subject incidence of treatment-emergent SAEs was Infections and Infestations (4.5% E/C/F/TAF, 0% E/C/F/TDF). No deaths or pregnancies occurred.

Table 1-7. GS-US-292-0102: Treatment-Emergent Adverse Events: Overall Summary, Safety Analysis Set

	E/C/F/TAF (N = 112)	E/C/F/TDF (N = 58)
Subjects Experiencing Any Treatment-Emergent Adverse Event	91 (81.3%)	47 (81.0%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	42 (37.5%)	17 (29.3%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	8 (7.1%)	2 (3.4%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event	38 (33.9%)	15 (25.9%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event	6 (5.4%)	1 (1.7%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	1 (0.9%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	6 (5.4%)	2 (3.4%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event	0	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	4 (3.6%)	0
Subjects who had Treatment-Emergent Death	0	0

Treatment-emergent death refers to a death occurring between the first dose date and the last dose date plus 30 days (inclusive).

At least 1 treatment-emergent laboratory abnormality (ie, at least 1 grade level increase in graded abnormality) was reported for 103/111 subjects (92.8%) in the E/C/F/TAF group and 46/58 subjects (79.3%) in the E/C/F/TDF group. The majority of laboratory abnormalities were Grade 1 or 2 in severity. Subject incidence of Grade 3 or 4 treatment-emergent laboratory abnormalities is summarized in Table 1-8.

Table 1-8. GS-US-292-0102: Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities, Safety Analysis Set

	E/C/F/TAF (N = 112)	E/C/F/TDF (N = 58)
Maximum Post-Baseline Toxicity Grade 3 or 4	19 (17.1%)	8 (13.8%)
Neutrophils	5 (4.5%)	1 (1.7%)
WBC	1 (0.9%)	0
Amylase	2 (1.8%)	1 (1.7%)
Creatine Kinase (CK)	6 (5.4%)	2 (3.4%)
Lipase	0	1 (12.5%)
Serum Glucose (Hyperglycemia)	0	1 (1.7%)
Total Cholesterol (Fasting, Hypercholesterolemia)	1 (0.9%)	0
Triglycerides (Fasting)	1 (0.9%)	1 (1.7%)
LDL (Fasting)	7 (6.4%)	2 (3.4%)
Urine Protein (Proteinuria)	1 (0.9%)	0
Urine RBC (Hematuria, Quantitative)	1 (0.9%)	0

Denominator for percentage is the number of subjects in the SAS with at least 1 post-baseline laboratory value (for the test).
Subjects were counted once for the maximum postbaseline severity for each laboratory test.
Lipase test was only performed for subjects with serum amylase > 1.5 × upper limit of normal.
Urine RBC (hematuria, quantitative) was graded based on DAIDS grading scale (with the modification of urine RBC > 75 cells/HPF as Grade 3).
For Urinalysis (i.e., urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.

No clinically significant changes in mean thyroid function tests (TSH, free T3, free T4) or serum immunoglobulins (IgG and IgM) were observed.

1.2.4.6.2. Renal Safety

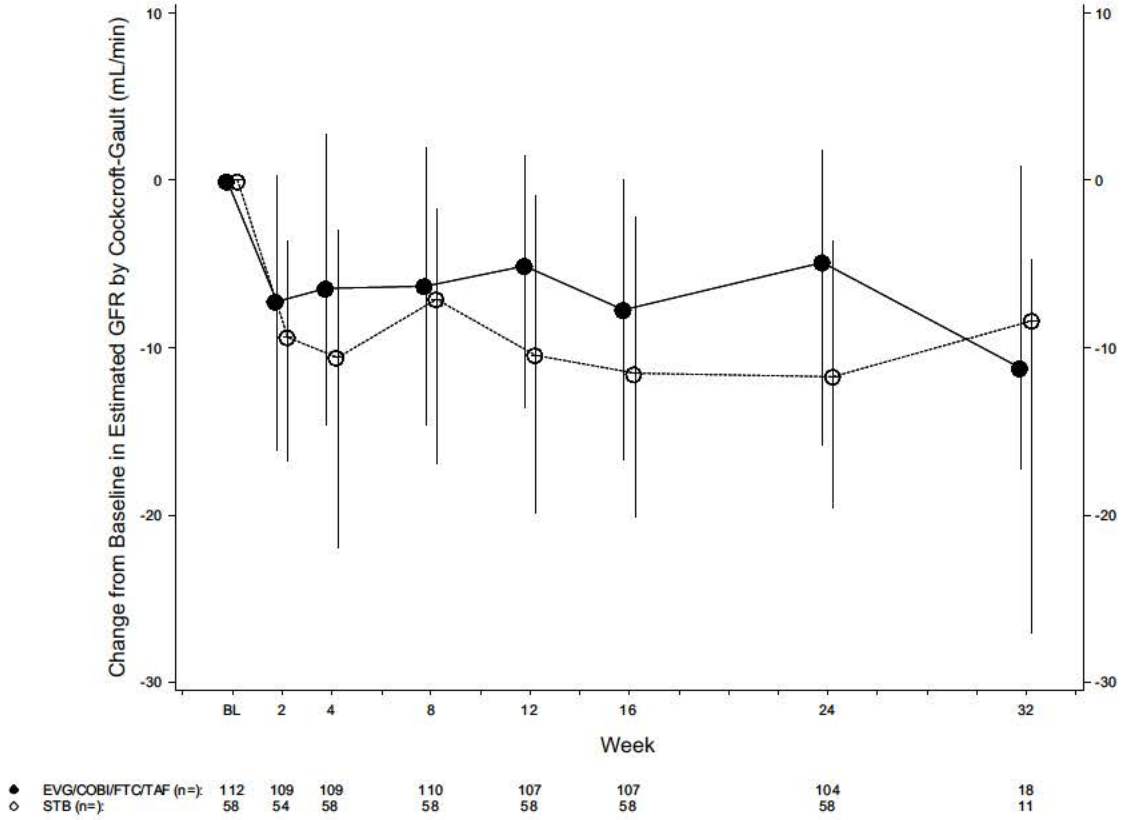
On multiple objective laboratory tests of renal function, subjects receiving E/C/F/TAF had a lower magnitude of change than subjects receiving E/C/F/TDF through 24 weeks.

The change from baseline in serum creatinine (sCr) was lower in the E/C/F/TAF group compared to the E/C/F/TDF group at most assessments through Week 24. At Week 24, median change from baseline in serum creatinine was 0.07 mg/dL (range through Week 24: 0.05 mg/dL to 0.08 mg/dL) for the E/C/F/TAF group and 0.11 mg/dL (range through Week 24: 0.08 mg/dL to 0.11 mg/dL) for the E/C/F/TDF group (Week 24 p = 0.016).

Accordingly, the decrease from baseline in estimated glomerular filtration rate (GFR) by Cockcroft-Gault formula for CL_{Cr} was lower in the E/C/F/TAF group compared to the E/C/F/TDF group at most assessments through Week 24 (Figure 1-5). At baseline, the mean (SD) estimated GFR_{C-G} was similar between groups (120.1 [30.22] (mL/min) for subjects in the E/C/F/TAF group and 114.7 [21.68] (mL/min) for subjects in the E/C/F/TDF group. At Week 24,

median change from baseline estimated GFR_{C-G} was 6.6 mL/min for the E/C/F/TAF group and 10.6 mL/min for the E/C/F/TDF group (p = 0.009). At Week 24, 3 (5.2%) subjects in the E/C/F/TDF group would be classified as new Stage 3 CKD (eGFR 30-59 mL/min) vs. 1 (1.0%) subjects in the E/C/F/TAF group, and 15 (14.4%) subjects in the E/C/F/TAF group would be classified as new Stage 2 CKD (eGFR 60-89 mL/min) vs. 20 (34.5%) subjects in the E/C/F/TDF group.

Figure 1-5. GS-US-292-0102: Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault by Visit, Safety Analysis Set



At Week 24, a trend towards reduced proteinuria was observed in the E/C/F/TAF group. By urine dipstick, the frequency of maximum post-baseline proteinuria (any grade) was 13.5% in E/C/F/TAF vs. 20.7% in E/C/F/TDF. The median change from baseline in urine albumin to creatinine ratio (UACR) was 0.84 mg/g in E/C/F/TAF vs 0.07 in E/C/F/TDF. The median change from baseline in urine protein to creatinine ratio (UPCR) was 5.6 mg/ g and 1.6 mg/g in the E/C/F/TAF and E/C/F/TDF groups, respectively. CCI [redacted] At Week 24, median change from baseline beta-2-microglobulin to creatinine ratio was 35.9 µg/g for E/C/F/TAF vs 1.1 µg/g for E/C/F/TDF (p = 0.004), and median change from baseline in retinol binding protein to creatinine ratio was 0.7 µg/g for E/C/F/TAF vs 11.9 µg/g for E/C/F/TDF (p = 0.006).

A treatment difference for other laboratory markers of kidney function were not observed, including median change from baseline for serum phosphate and fractional excretion of phosphate (fractional excretion of phosphate [FEPO4] using adjusted sCr).

1.2.4.6.3. Bone Safety

DXA scans of the spine and hip were performed at the Baseline and Week 24 visits (and at the early study drug discontinuation visit, if applicable) to measure changes from baseline in BMD.

The percent changes from baseline in BMD values in the lumbar spine and hip are summarized in Table 1-9. The median percentage decrease from baseline was significantly less for subjects in the E/C/F/TAF group compared with that for subjects in the E/C/F/TDF group for both spine ($p = 0.002$) and hip ($p < 0.001$) BMD.

The categorical distribution of subjects in each treatment group with percentage changes in BMD from baseline within specified ranges at Week 24 is summarized for spine and hip in Table 1-10. At Week 24, a significantly higher proportion of subjects in the E/C/F/TAF group than in the E/C/F/TDF group had no decreases in BMD at the hip (40.6% vs 22.8%; $p < 0.001$) and spine (37.5% vs 12.1%; $p = 0.003$). Substantially fewer subjects in the E/C/F/TAF group had decreases in BMD of >3% at the hip than in the E/C/F/TDF group (3.0% vs 31.6%) at Week 24.

Table 1-9. GS-US-292-0102: Percent Change from Baseline in Lumbar Spine and Hip Bone Mineral Density at Week 24, DXA Analysis Set

	E/C/F/TAF[a] (N = 101-104)	E/C/F/TDF[a] (N = 57-58)	E/C/F/TAF vs E/C/F/TDF p-value
Change at Week 24			
Spine			
N	104	58	0.002
Mean (SD)	-0.84 (3.411)	-2.48 (2.519)	
Median (Q1, Q3)	-0.92 (-3.00, 0.99)	-2.34 (-3.65, -0.33)	
Min, Max	-8.49, 17.12	-10.37, 2.43	
Hip			
N	101	57	< 0.001
Mean (SD)	-0.30 (1.774)	-2.103 (2.677)	
Median (Q1, Q3)	-0.42 (-1.44, 0.71)	-2.08 (-3.60, -0.48)	
Min, Max	-4.68, 7.84	-8.55, 4.86	

P-values were from the Wilcoxon rank sum test.
a Only subjects with nonmissing spine or hip BMD for the baseline visit and at least 1 E/C/F/TDF post baseline visit were included in the CCI analysis set.

Table 1-10. GS-US-292-0102: Percent Change in Bone Mineral Density by Gradation at Week 24, DXA Analysis Set

	E/C/F/TAF[a] (N = 101-104)	E/C/F/TDF[a] (N = 57-58)	E/C/F/TAF vs E/C/F/TDF p-value
Percentage Change at Week 24			
Spine			
No Decrease	39/104 (37.5%)	7/58 (12.1%)	0.003
> 0 to < = 1% Decrease	14/104 (13.5%)	11/58 (19.0%)	
> 1 to < = 3% Decrease	25/104 (24.0%)	17/58 (29.3%)	
> 3 to < = 5% Decrease	18/104 (17.3%)	15/58 (25.9%)	
> 5% Decrease	8/104 (7.7%)	8/58 (13.8%)	
Hip			
No Decrease	41/101 (40.6%)	13/57 (22.8%)	< 0.001
> 0 to < = 1% Decrease	23/101 (22.8%)	7/57 (12.3%)	
> 1 to < = 3% Decrease	34/101 (33.7%)	19/57 (33.3%)	
> 3 to < = 5% Decrease	3/101 (3.0%)	12/57 (21.1%)	
> 5% Decrease	0/101	6/57 (10.5%)	

P-value was from the CMH test for ordinal data (row mean scores differ statistic was used).
a Only subjects with nonmissing spine or hip BMD for the baseline visit and at least 1 postbaseline visit were included in CCI analysis set.

Clinical BMD status was assessed using BMD T-scores. Changes from baseline in BMD status at Week 24 were determined using T-scores. At Week 24, 6 of 99 subjects (6.1%) in the E/C/F/TAF group and 2 of 58 subjects (3.4%) in the E/C/F/TDF group showed a deterioration from baseline in spine BMD T-score category, and 1 of 99 subjects (1.1%) in the E/C/F/TAF group and 5 of 54 subjects (9.3%) in the E/C/F/TDF group showed a deterioration from baseline in hip BMD T-score category. In the E/C/F/TAF group at Week 24, 5 subjects had improvement in spine BMD T-score category and 1 subject had improvement in hip BMD T-score category. One subject in the E/C/F/TDF group showed improvement in the hip BMD T-score category. As a continuous variable, median decrease from baseline BMD T-score was significantly less for E/C/F/TAF vs E/C/F/TDF at both spine (-0.08 vs. 0.22, p = 0.005) and hip (0.03 vs 0.14, p < 0.001).

Bone turnover markers, including one for bone resorption (C-type collagen sequence [CTX]) and three for formation (bone specific alkaline phosphatase [bsAP], osteocalcin [OC], and procollagen type 1 N-terminal propeptide [P1NP]), were assessed to support the BMD data. Comparisons of percent change from baseline for each bone turnover marker at Weeks 12 and 24 demonstrated statistically significantly less change in the E/C/F/TAF arm, and provide evidence of less bone turnover at both timepoints in the E/C/F/TAF arm vs the E/C/F/TDF arm (Table 1-11). These results are consistent with the observations made in the BMD analyses.

Table 1-11. GS-US-292-0102: Percentage Change from Baseline in Bone Turnover Markers, Safety Analysis Set

	E/C/F/TAF (N = 112)	E/C/F/TDF (N = 58)	E/C/F/TAF vs E/C/F/TDF p-value
Week 12			
CTx, % change in mean (SD)	37.9 (62.0)	103.7 (109.1)	<0.001
bsAP, % change in mean (SD)	-13.4 (16.0)	2.0 (16.3)	<0.001
OC, % change in mean (SD)	22.0 (32.5)	46.9 (49.1)	<0.001
P1NP, % change in mean (SD)	2.6 (32.2)	30.1 (36.1)	<0.001
Week 24			
CTx, % change in mean (SD)	39.2 (79.2)	94.8 (107.9)	<0.001
bsAP, % change in mean (SD)	4.1 (17.2)	25.3 (24.9)	<0.001
OC, % change in mean (SD)	30.3 (43.5)	71.0 (74.3)	<0.001
P1NP, % change in mean (SD)	10.6 (38.7)	58.8 (61.4)	<0.001

P-values were from the Wilcoxon rank sum test; CTx = Type 1 collagen crosslinked C-telopeptide;
bsAP = serum bone specific alkaline phosphatase; OC = osteocalcin; P1NP = procollagen Type 1 N-terminal propeptide.

1.2.4.6.4. Week 24 Conclusions

Key conclusions from the Week 24 analysis of Study GS-US-292-0102 included the following:

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 was similar between treatment groups
- Treatment was generally well tolerated as most AEs were mild and not associated with treatment discontinuation. No new or unexpected adverse events occurred.
- The data shows that subjects taking E/C/F/TAF had more modest changes in creatinine and in bone mineral density than subjects taking E/C/F/TDF. The differences were statistically significant and may have important clinical relevance for individual subjects.

Other than renal lab abnormalities and biomarkers and bone biomarkers, the frequency and type of laboratory abnormalities was comparable between the two treatment arms.

1.3. Rationale for This Study

1.3.1. Tenofovir Alafenamide (TAF) for Treatment of Chronic Hepatitis B

Approximately one-third of the world's population has serological evidence of past or present HBV infection with over 350 million people globally who are chronic HBV surface antigen (HBsAg) carriers. The disease burden for HBV varies regionally, with greater than 50% of all subjects residing in Asian countries with the highest prevalence (e.g. China, India, Vietnam, Indonesia, South Korea, Taiwan, the Philippines, and Pakistan). The primary goal of treatment is to achieve and maintain virologic suppression, without resistance, which has been shown to

translate to improvement in liver disease outcomes. Current guidelines recommend treatment for subjects with evidence of ongoing viral replication along with liver injury based on elevated levels of serum ALT.

TDF and ETV are highly potent first line therapies for CHB; however, each has specific limitations. TDF has a potential to cause renal- and bone-related toxicities in a subset of subjects. ETV has reduced activity in drug-treated populations, specifically lamivudine-experienced/resistant subjects {Baldick 2008, Tenney 2009}. The latter is a key limitation for ETV use as LAM remains one of the most commonly prescribed HBV treatments in most regions of the world. Thus, despite the availability of effective treatments there remains a clear need for newer oral HBV agents that are safe and well tolerated for long term use, and capable of achieving high rates of viral suppression with little or no potential for resistance development.

Tenofovir alafenamide (TAF), a novel prodrug of TFV, has the potential to further advance the treatment of chronic HBV infection. In contrast to TDF, an agent that is rapidly and completely cleaved by intestinal and plasma esterases to TFV, TAF is a more stable prodrug that efficiently resists early enzymatic cleavage following oral administration and remains more fully intact until it is taken up by target cells. As a consequence, TAF, when given at a lower dose than TDF, is capable of efficiently delivering active drug (e.g. TFV-DP) to the virally-infected cells (e.g. HBV-infected hepatocytes and HIV-infected lymphoid cells) while systemic exposures of TFV are reduced compared with oral administration of TDF 300 mg. These features are hypothesized to translate into the potential for effective suppression of viral replication, and an improved tolerability and safety profile.

Results from GS-US-320-0101, a Phase 1b study evaluating the short-term (28 day) safety, efficacy (HBV DNA suppression), and PK of TAF at 4 dose levels (8 mg, 25 mg, 40 mg, and 120 mg) compared to TDF 300 mg, has shown no dose effect in regard to viral suppression, and similar short-term safety and tolerability compared with TDF. Intensive PK results show 93% or greater reductions in TFV exposures with doses of TAF 25 mg or lower compared to the TFV exposures generated with TDF 300 mg. These results, taken together with 24 weeks safety results from the HIV Phase 2 study GS-US-292-0102, which directly compares TAF to TDF (each included as a component of an STR), suggest that TAF is safe and well tolerated and may have a lower potential for renal- and bone-related AEs compared to TDF. Importantly, TFV exposures for E/C/F/TAF 10 mg are comparable to TFV exposures generated with TAF 25 mg given as a stand alone agent.

1.3.2. Rationale for the Current Study

TDF and ETV are highly potent first line therapies for chronic HBV; however, each has specific limitations. TDF has a potential to cause renal- and bone-related toxicities in a subset of subjects. ETV has reduced activity in drug-treated populations, specifically lamivudine (LAM)-experienced/resistant subjects. Thus, despite the availability of effective treatments there remains a clear need for newer oral HBV agents that are safe and well tolerated for long term use, and capable of achieving high rates of viral suppression with little or no potential for resistance development. TAF has the potential to address each of these requirements.

The current study is designed to evaluate non-inferiority of TAF compared to TDF in regard to the proportion of subjects with HBV DNA levels below 29 IU/mL at Week 48. The durability of TAF compared to TDF in regard to the proportion of subjects with HBV DNA < 29 IU/mL at Weeks 96 and 144 will also be assessed in a double blind fashion. In addition to treatment naïve subjects, treatment experienced CHB subjects who are viremic and with elevated ALT levels at screening are included. This is based on given results from GS-US-174-0106 (ADV suboptimal responders) and GS-US-174-0121 (LAM-resistant subjects) which demonstrated in viremic patients comparable rates of HBV DNA suppression, as described below, in comparison to results in mostly treatment naïve subjects participating in pivotal studies GS-US-174-0102 (HBeAg-negative subjects) and GS-US-174-0103 (HBeAg-positive subjects). Given the unique properties of TAF (efficient delivery of the active moiety, TFV-DP, to HBV-infected hepatocytes with reduced systemic TFV exposures), this study will also evaluate the potential safety differences (e.g. renal- and bone-related complications) of TAF relative to TDF at Week 48 and long term comparative safety at Week 96 and 144, after which subjects will be further evaluated for longer-term safety and efficacy of TAF in an open-label TAF 25 mg QD extension phase through Week 384. The extension phase is important as it will enable the evaluation of subjects treated for the entire 384 week period with TAF as well as those who received 144 weeks of TDF initially in a double-blinded fashion followed by an additional 240 weeks of open-label TAF. The latter group will allow an ongoing assessment, including possible resolution, of any potential bone- and/or renal-related (or other) complications during TAF treatment that might have arisen under initial treatment with TDF.

The primary endpoint of this study is the proportion of subjects with HBV DNA < 29 IU/mL at Week 48; the lowest limit of susceptibility of the polymerase chain reaction (PCR) assay to be employed (Roche COBAS® Taqman® HBV test for use with the High Pure System). A histological component of treatment response is not included. Alternatively, non-invasive means (i.e. Fibrotest®) will be used to assess the degree of fibrosis at baseline and the change in fibrosis on an annual basis for all subjects participating in the trial. In support of this, 48 week results from studies, GS-US-174-0102 and GS-US-174-0103, which formed the basis for TDF approval for CHB, showed TDF to be superior to ADV based on a “complete response” to treatment (a composite endpoint of HBV DNA suppression and histologic improvement based on repeat liver biopsy). In GS-US-174-0102, conducted in HBeAg-negative (presumed pre-core mutant) subjects, 70.8% and 48.8% of subjects randomized to TDF and ADV, respectively, achieved a complete response at Week 48 (treatment difference: 23.5%; $p < 0.001$). Of the components, HBV DNA suppression (< 69 IU/mL) was achieved in 94.4% and 64.0% (treatment difference: 30.3%; $p < 0.001$), while histologic improvement was achieved in 74.2% and 68.8% (treatment difference: 5.2%; $p = 0.292$) of TDF- and ADV-treated subjects, respectively. Thus, the greater potency of TDF relative to ADV resulting in a significantly higher rate of viral suppression was the primary element associated with the superior treatment response at 48 weeks {Marcellin 2007, Marcellin 2008}. Similar findings were observed in HBeAg-positive subjects in GS-US-174-0103.

After 48 weeks, subjects in GS-US-174-0102 and GS-US-174-0103 were eligible to continue open-label treatment with TDF. At Year 5 (Week 240), 331/641 (52%) of subjects on TDF (without addition of FTC) underwent a repeat liver biopsy, and regression of fibrosis

(improvement in Ishak fibrosis score of ≥ 1 point) was seen in 52% (172/331) of subjects. Furthermore, in 94/331 (28%) subjects with cirrhosis (Ishak score ≥5) at baseline, 73% (69/94) were no longer cirrhotic at year 5 (≥ 1 unit decrease in Ishak score). These results confirm the benefits of long term viral suppression with TDF in terms of regression of fibrosis and reversal of cirrhosis in the majority of TDF-treated subjects {Marcellin 2013}.

The efficacy of TDF in viremic treatment experienced CHB populations has been shown to be similar to treatment naïve subjects. In a prospective, randomized (1:1), double-blind, Phase 3b study (GS-US-174-0121) which compared TDF alone to the combination of FTC/TDF in 280 HBeAg-positive and HBeAg-negative subjects receiving treatment with LAM and having HBV DNA > 3 $\log_{10}$ IU/mL with documented LAM-resistance (rtM204I/V ± rtL180M mutation[s]), 89.4% of TDF-treated subjects vs. 86.3% treated with FTC/TDF had HBV DNA < 69 IU/mL at Week 96 (primary endpoint, missing equals failure analysis; p = 0.43). BMD was also assessed in GS-US-174-0121, and small declines in BMD (< 2%) of both hip and spine were seen with equal frequency in both groups which occurred by Week 24 (spine) and Week 72 (hip). In another prospective, randomized, double-blind study of TdF vs. FTC/TDF in 105 HBeAg-positive and HBeAg-negative subjects with a prior suboptimal response to ADV (GS-US-174-0106), no differences in HBV DNA suppression (proportion less than 69 IU/mL) were seen between treatment groups (82.4% TDF vs. 84.0% FTC/TDF; ITT, non-completer equals failure; p = 0.78). Taken together, these studies support the efficacy of TDF in treatment experienced subjects as being similar to results seen in treatment naïve subjects.

1.3.3. Rationale for Dose Selection

In the Phase 1b study, GS-US-320-0101, which has completed enrollment, 4 doses (8, 25, 40, and 120 mg) of TAF monotherapy, and TDF 300 mg were evaluated in 51 treatment naïve CHB subjects. To date, all subjects have completed the 28 day dosing period. Results demonstrate that TAF when given in doses over a range of 8 to 120 mg results in similar HBV DNA declines over 28 days. Furthermore, HBV DNA suppression with TAF is comparable to that of TDF 300 mg. In GS-US-320-0101, increased rates of viral suppression were not observed with higher TAF doses (40 mg, 120 mg) relative to lower TAF doses (8 mg and 25 mg), and similar safety profiles were observed among TAF treatment groups. PK results demonstrate a 93% reduction in TFV exposures relative to TDF 300 mg when TAF is dosed at 25 mg. These results in CHB subjects are consistent with data in healthy volunteers and HIV-infected subjects given TAF 25 mg as a stand alone agent. Importantly, as previously stated, the TFV exposures seen with TAF 25 mg in CHB subjects are therapeutically comparable to those in HIV patients receiving E/C/F/TAF 10 mg (due to an inhibitory drug-drug interaction between TAF and COBI when these agents are included in the E/C/F/TAF STR) which provide safety data (from Phase 2 study GS-US-292-0102) supporting the development of TAF for hepatitis B at the 25 mg dose level. Further, in CHB subjects participating in the Phase 1b study who were dosed at the lowest TAF dose (8 mg), a 97% reduction in TFV exposures relative to TDF 300 mg was observed, representing an incremental reduction in TFV exposure of only 5% at this dose level relative to TAF 25 mg.

Importantly, the TFV exposures at a 25 mg dose when given alone are consistent with TAF exposures generated with the E/C/F/TAF 10 mg STR currently in Phase 3 development for treatment of HIV infection. Thus, the efficacy and safety of TAF in HIV is also being evaluated at a dose level that is therapeutically equivalent to the dose selected for study GS-US-320-0108.

Final Week 24 results from GS-US-292-0102, a phase 2 study being conducted in HIV-1 treatment naïve subjects, demonstrated similar safety and tolerability of TAF vs. TDF when each is included as a component of STRs containing elvitegravir, cobicistat, and emtricitabine. At Week 24, significant differences were noted between arms in regard to smaller declines in hip BMD, estimated CL_{Cr} (Cockcroft-Gault), and changes in various biomarkers of bone and renal function which are suggestive of differences in bone and renal tolerability of TAF vs. TDF. Similar assessments are included in the present trial in HBeAg-negative, chronic HBV subjects, and the study is sufficiently powered to demonstrate a potentially superior safety profile for TAF relative to TDF in regard to these bone and renal parameters.

In summary, a 25 mg dose was selected for TAF for use in this non-inferiority trial based upon the safety profile for TAF in treatment naïve HIV-1-infected subjects from GS-US-292-0102, which utilizes a therapeutically equivalent TAF dose (10 mg as a component of the E/C/F/TAF STR), the viral suppression results in chronic HBV subjects in GS-US-320-0101 showing comparable rates of HBV DNA decline for a TAF 25 mg dose compared to TDF 300 mg (the approved dose for treatment of HBV), and the reduced systemic TFV exposures (~93%) seen with TAF relative to TDF 300 mg, when dosed at this level.

1.4. 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 compare the efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment-naïve and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL

- To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment naïve and treatment experienced subjects

The key secondary safety objectives of the study are:

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the percent change from baseline in hip and spine BMD at Week 48

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the change from baseline in serum creatinine at Week 48

Other secondary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Weeks 96 and 144

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL (target not detected) at Weeks 48, 96, and 144

- To compare the biochemical (ALT normalization by central laboratory and AASLD criteria) response of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the serological response (loss of HBsAg with seroconversion to anti-HBs) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the change in fibrosis as assessed by FibroTest® of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the incidence of drug resistant mutations of TAF 25 mg QD versus TDF 300 mg QD at Weeks 48, 96, and 144

- To compare the change from baseline in ophthalmologic findings by fundoscopic examination of TAF 25 mg QD versus TDF 300 mg QD at Weeks 24, 48, 72 , 96, and 144 (or ED visit if prior to Week 144 and more than 24 weeks since prior exam) in a subset of subjects

- To characterize the pharmacokinetics of TAF and tenofovir (TFV) and determine intracellular concentrations of tenofovir diphosphate (TFV-DP) within peripheral blood mononuclear cells (PBMC) in subjects receiving TAF or TDF

- To evaluate the comparative open-label efficacy, safety, and the incidence of drug resistance mutations of TAF 25 mg QD in subjects initially randomized to TAF 25 mg QD and in subjects sequentially treated with TDF 300 mg QD and then switched to open-label TAF 25 mg QD

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is a randomized, double-blind, non-inferiority study to compare the antiviral activity of TAF 25 mg QD versus TDF 300 mg QD. Approximately three hundred ninety (390) subjects will be randomized in a 2:1 ratio (A:B) to the treatment arms for 144 weeks (96 weeks under Amendment 2.1), and will be stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naïve vs. treatment-experienced).

For China, approximately 150 additional subjects will be randomized in a 2:1 ratio (A: B) to the treatment arms for 96 weeks, and will be stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naïve vs. treatment-experienced).

If the subject is deemed ineligible for this study by HBV serology (i.e. HBeAg positive CHB), this information may be used to determine eligibility for GS-US-320-0110 (another Gilead Sciences Phase 3 study in HBeAg positive, CHB subjects; this study must also be IRB/EC approved at the participating center).

Treatment Arm A: 260 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD
Treatment Arm B: 130 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD

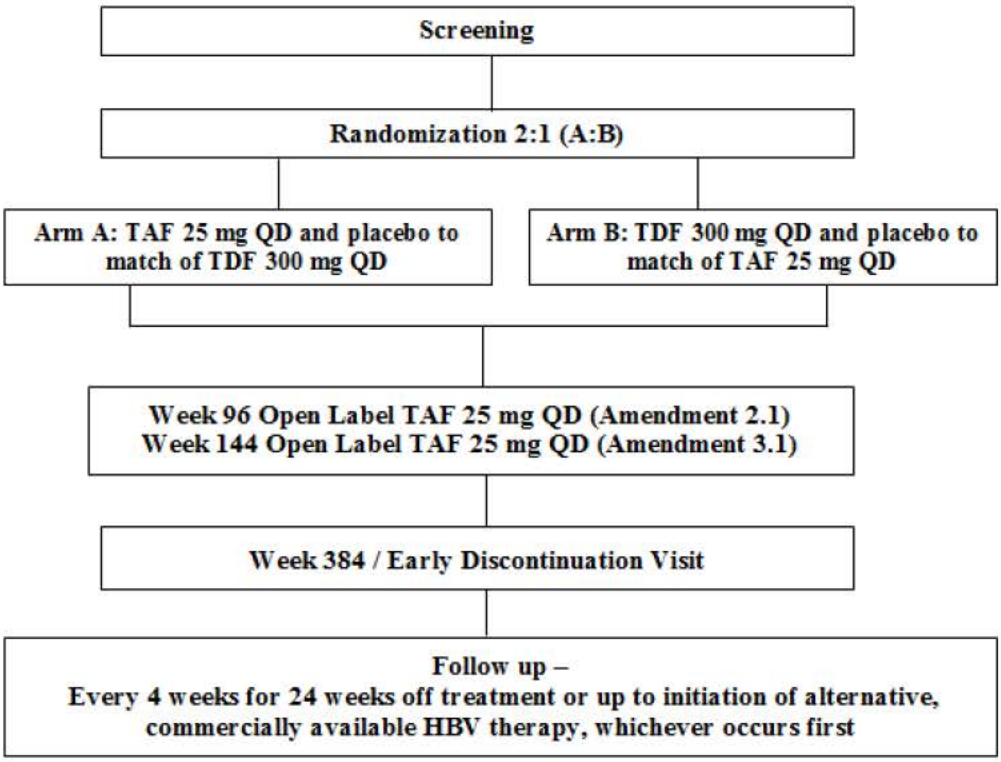
For China, approximately 150 additional subjects (100 in Treatment Arm A and 50 in Treatment Arm B) will be enrolled for local registration purposes.

Subjects with a history of or current diagnosis of compensated cirrhosis are eligible for enrollment. Acceptable diagnostic criteria for cirrhosis include a Metavir or Knodell fibrosis score ≥ 4 or Ishak fibrosis score ≥ 5 by liver biopsy, or previous Fibroscan result > 12kPa (in countries where locally approved). Available information regarding the presence or absence of cirrhosis by these criteria will be captured in the electronic case report forms at Baseline, and any other time during the trial should an investigator opt to undertake additional studies. Importantly, the change in fibrosis as assessed by Fibrotest® will be performed in all subjects participating in the trial at Baseline, and annually thereafter through Week 384/ED.

The duration of double-blind treatment is 144 weeks (96 weeks under Amendments 2.1). At Week 144, all subjects remaining on blinded treatment will be switched to the open-label TAF 25 mg QD extension period for up to an additional 240 weeks (Week 144 through Week 384/ED). Subjects already assigned to open-label TAF 25 mg QD at Week 96 per Amendment 2.1 will continue on open-label TAF 25 mg QD through Week 384/ED. All subjects who complete the double-blind period of treatment are eligible for participation in the open label TAF 25 mg QD extension period. Subjects who permanently discontinue study drug (either prematurely [ED] or at the end of study [Week 384]) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs, will be followed every 4 weeks for 24 weeks off treatment or until initiation of alternative, commercially available HBV therapy, whichever occurs first.

Subjects with HBsAg loss with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion to anti-HBs prior to Week 48 are not permitted to discontinue study drug prior to the Week 48 visit. After Week 48, these subjects who discontinue study drug will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule (Appendix 2) through Week 384/ED. Discontinuation of study drug for subjects 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.

Figure 3-1. Study Schema



3.2. Biomarker Testing

3.2.1. Biomarker Samples to Address the Study Objectives:

CCI

.CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 390 subjects, who are 18 years of age and older, with HBeAg-negative chronic hepatitis B will be randomized 2:1 to receive either blinded TAF 25 mg and TDF 300 mg matched placebo (n = 260) or TDF 300 mg and TAF 25 mg matched placebo (n = 130) for 144 weeks (96 weeks under Amendment 2.1).

For China, approximately 150 subjects, who are 18 years of age and older, with HBeAg-negative chronic hepatitis B will be randomized 2:1 to receive either blinded TAF 25 mg and TDF 300 mg matched placebo (n = 100) or TDF 300 mg and TAF 25 mg matched placebo (n = 50) for 96 weeks.

4.2. Inclusion Criteria

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

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

2) Male and non-pregnant, non-lactating female subjects, 18 years of age and older, 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 6).

3) Documented evidence of chronic HBV infection (e.g. HBsAg positive for more than 6 months).

4) HBeAg-negative, chronic hepatitis B with all of the following:

   a) HBeAg-negative and HBeAb-positive at Screening (if the subject is deemed ineligible for this study by HBV serology [i.e. HBeAg-positive CHB], this information may be used to determine eligibility for GS-US-320-0110 [another Gilead Sciences Phase 3 study in HBeAg-positive, CHB subjects; this study must also be IRB/EC approved at the participating center])

   b) Screening HBV DNA $\geq 2 \times 10^4$ IU/mL

   c) Screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and $\leq 10 \times$ ULN (by central laboratory range)

5) Treatment-naïve subjects (defined as < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue), **OR** treatment-experienced subjects (defined as subjects meeting all entry criteria [including HBV DNA and serum ALT criteria] and with $\geq$ 12 weeks of previous treatment with any nucleoside or nucleotide analogue) will be

eligible for enrollment. Treatment-experienced subjects receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization, when it will be discontinued.

6) Any previous treatment with interferon (pegylated or non-pegylated) must have ended at least 6 months prior to the baseline visit.

7) Estimated creatinine clearance (CL_{Cr}) ≥ 50 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the Screening evaluation, as follows:

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

[Note: multiply estimated rate by 0.85 for women]

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

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

4.3. Exclusion Criteria

Subjects who meet ***any*** of the following exclusion criteria are not to be enrolled in this study.

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. For a list of protocol-specified contraceptive methods, refer to Appendix 6.

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

4) Evidence of hepatocellular carcinoma (e.g. as evidenced by recent imaging)

5) Any history of, or current evidence of, clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage).

6) Abnormal hematological and biochemical parameters, including:

   a) Hemoglobin < 10 g/dL

   b) Absolute neutrophil count < 750/mm^3

   c) Platelets ≤ 50,000/mm^3

   d) AST or ALT > 10 × ULN

e) Total Bilirubin > 2.5 × ULN

f) Albumin < 3.0 g/dL

g) INR > 1.5 × ULN (unless stable on anticoagulant regimen)

7) Received solid organ or bone marrow transplant.

8) Significant renal, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator.

9) Significant bone disease (e.g., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses), or multiple bone fractures.

10) Malignancy within the 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.

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

12) Known hypersensitivity to study drugs, metabolites, or formulation excipients.

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

14) 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.

15) Subjects on prohibited concomitant medications (See Table 5-1). Subjects on prohibited medications, otherwise eligible, will need a wash out period of at least 30 days.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

A centralized randomization procedure via an Interactive Voice/Web Response System (IVRS/IWRS) will be used for this study, whereby study treatment will be assigned to subjects according to the randomization schedule. A unique subject number will be provided during randomization. If the subject is deemed ineligible for this study by HBV serology (i.e. HBeAg-positive CHB), this information may be used to determine eligibility for GS-US-320-0110 (another Gilead Sciences Phase 3 study in HBeAg-positive, CHB subjects; this study must also be IRB/EC approved at the participating center). Eligible subjects will be randomized 2:1 to receive either blinded TAF 25 mg and TDF matched placebo or TDF 300 mg and TAF matched placebo for 144 weeks (96 weeks under Amendment 2.1). Subjects will be stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 $\log_{10}$ IU/mL - < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naïve vs. treatment-experienced). At Week 144, all subjects will be switched to open label TAF 25 mg QD up to an additional 240 weeks (Week 144 through Week 384/ED). Subjects already assigned to open-label TAF 25 mg QD at Week 96 per Amendment 2.1 will continue on TAF through Week 384/ED. For the entire duration of the study, subjects and investigator will remain blinded to the initial treatment regimen to which the subjects were randomized.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IVRS/IWRS for that subject. Gilead recommends, but does not require that the investigator contact the Gilead Medical Monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead Medical Monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Pharmacovigilance and Epidemiology (PVE)may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Tenofovir Alafenamide (TAF), Tenofovir Disoproxil Fumarate (TDF) and Matched Placebos

5.2.1. Formulation

5.2.1.1. Tenofovir Alafenamide (TAF) Tablets

TAF 25 mg tablets contain 28 mg of tenofovir alafenamide fumarate, which is equivalent to 25 mg of tenofovir alafenamide (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.

5.2.1.2. Placebo to match TAF Tablets

Placebo tablets to match TAF 25 mg are yellow, round-shaped, and film-coated. The tablets are debossed with "GSI" on one side and "25" on the other side. Each 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.

5.2.1.3. Tenofovir Disoproxil Fumarate (Viread®, Tenofovir DF, TDF)

TDF 300 mg tablets contain 300 mg of tenofovir disoproxil fumarate (TDF), which is equivalent to 245 mg of tenofovir disoproxil. The tablets are light blue, almond-shaped, plain-faced, and film-coated. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose (hydroxypropyl methylcellulose), glycerol triacetate, titanium dioxide, and indigo carmine aluminum lake.

5.2.1.4. Tenofovir Disoproxil Fumarate (Viread®, Tenofovir DF, TDF) to be Used in Developing Markets

TDF 300 mg tablets to be used in developing markets contain 300 mg of tenofovir disoproxil fumarate (TDF), which is equivalent to 245 mg of tenofovir disoproxil. The tablets are white, almond-shaped, film-coated, debossed with "GILEAD" and "4331" on one side and plain-faced on the other side. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, triacetin and titanium dioxide.

5.2.1.5. Placebo to match TDF Tablets

Placebo tablets to match TDF 300 mg are light blue, almond-shaped, plain-faced, film-coated tablets. Each tablet contains the following inactive ingredients: denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The film coating contains the following inactive ingredients: lactose monohydrate, hypromellose (hydroxypropyl methylcellulose), triacetin, titanium dioxide, and indigo carmine aluminum lake.

5.2.1.6. Placebo to Match TDF Tablets to be Used in Developing Markets

Placebo tablets to match TDF 300 mg for developing markets are white, almond-shaped, film-coated tablets, debossed with "GILEAD" and "4331" on one side and plain-faced on the other side. Each tablet contains the following inactive ingredients: denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The film coating contains the following inactive ingredients: lactose monohydrate, hypromellose, triacetin, and titanium dioxide.

5.2.2. Packaging and Labeling

TAF, TDF, and their matched placebo tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant and polyester coil. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

To ensure stability of the tablets and proper product identification, the drug should not be stored in a container other than the container in which it is supplied.

All labels for study drug bottles to be distributed to centers in the US, EU and the rest of the countries will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (July 2010) and/or other local regulations as applicable.

5.2.3. Storage and Handling

TAF, TDF, and their matched placebo tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F), inclusive. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.3. Dosage and Administration of TAF and TDF and Matched Placebos

Subjects will be randomly assigned (2:1) to receive one of the following treatments in a blinded fashion:

Treatment Arm A: 260 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD

Treatment Arm B: 130 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD

For China, approximately 150 additional subjects will be randomized 2:1 to receive either Treatment A (n = 100) or Treatment B (n = 50) for 144 weeks.

After 144 weeks of blinded randomized treatment (96 weeks under Amendment 2.1), each subject will switch to open-label TAF 25 mg QD for up to an additional 240 weeks (Week 144 through Week 384/ED). Subjects already assigned to open-label TAF 25 mg QD at Week 96 per Amendment 2.1 will continue on TAF through Week 384/ED.

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.

Observed in-clinic study drug dosing is required at Weeks 4 and 12 visits. Subjects who elect to dose in evening are not required to have in-clinic dosing and the single PK blood sample collection at the Week 4 and 12 visits.

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

5.4. Prior and Concomitant Medications

Concomitant/previous medications **taken within 30 days of screening**, up to and including the date of the visit 4 weeks after discontinuation of study treatment, need to be recorded in the source documents and eCRFs.

Concomitant use of some medications including herbal/natural products/therapies and over the counter medications with TAF may result in PK interactions.

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.

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:

- Nephrotoxic agents (e.g., aminoglycosides, amphoterecin 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, valacyclovir, ganciclovir, valganciclovir)

- Systemic chemotherapeutic agents, systemic corticosteroids (except short-term use of prednisone as a steroid burst [≤ 1 week of use], immunosuppressant, or immunomodulating agents
- Bisphosphonates
- Investigational agents (unless approved by Gilead Sciences)
- Medications excluded due to the potential for drug-drug interaction with TAF (Table 5-1)

Treatment-experienced subjects (defined as subjects meeting all entry criteria [including HBV DNA and serum ALT criteria] and with ≥ 12 weeks of previous treatment with any nucleoside or nucleotide analogue) receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization/Baseline/Day 1, when it will be discontinued.

Table 5-1. List of Medications That Are Prohibited or to Be Used with Caution Due to the Potential for Drug-Drug Interaction with Study Medication

Medication Class	Prohibited Medications	Medications to be used with caution
Analeptic	Modafinil	
Antiarrhythmics		Amiodarone, Quinidine: may increase concentration of TAF and/or TFV
Antibacterials		Clarithromycin: may increase concentration of TAF and/or TFV
Anticonvulsants		Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antifungals	Voriconazole	Itraconazole, Ketoconazole: may increase concentration of TAF and/or TFV
Antimycobacterials	Rifapentine, Rifabutin, Rifampin	
Calcium channel blockers		Diltiazem, Felodipine, Verapamil: may increase concentration of TAF and/or TFV
Digoxin		Digoxin: concomitant use may result in an increased or decreased level; use with caution and with appropriate monitoring of serum digoxin levels. Digoxin therapy should be initiated at the lowest dose, and the dose should be titrated to clinical response.
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	

5.5. Accountability for Tenofovir Alafenamide (TAF), Tenofovir Disoproxil Fumarate (TDF) and Matched Placebos

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product (IMP) kits and/or bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP kits and/or 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 kits and/or bottles
- Record the date, subject number, subject initials, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP kits and/or bottles returned, along with the initials of the person recording the information

5.5.1. 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 kits and/or 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.

Any deviation from protocol procedures should be documented and the sponsor or the contract research organization (CRO) should be notified.

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 be randomized within 45 days using an IVRS/IWRS. Subjects will receive study drugs within their assigned treatment group as described in Section 5.1. 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 Baseline to determine eligibility for participation in the study. The following will be performed and documented during the screening period:

- Obtain written informed consent
- Review of inclusion/exclusion criteria
- Obtain medical history, including HBV 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 including 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 spine and hip (at sites in China with capability only). DXA scan will be performed at any time during the Screening period and should be completed at least 14 days prior to the first dose of the study drug, in order to ensure an acceptable pre-dose DXA scan

- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) (CCI **only at select sites** - separate consent required) – to be performed at any time during the Screening period and prior to the first dose of the study drug

- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBeAg, HBeAb, HBsAg and reflex HBsAb), HIV-1, HDV, HCV, serum pregnancy test (for females of child-bearing potential), α-fetoprotein (AFP) and INR. An AFP > 50 ng/mL at Screening must have an appropriate evaluation (e.g. CT scan) in order to rule out HCC prior to being permitted to enter the study

- Estimated creatinine clearance (using the Cockcroft-Gault method)

- Urine sample for urinalysis

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 45 days for randomization into the study. If the subject is deemed ineligible for this study by HBV serology (i.e. HBeAg-positive CHB), this information may be used to determine eligibility for GS-US-320-0110 (another Gilead Sciences Phase 3 study in HBeAg positive, CHB subjects; this study must also be IRB/EC approved at the participating center).

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs 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

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

- Review concomitant medications
- Review adverse events
- Assess future risk of bone fracture using the Fracture Risk Assessment tool (FRAX®; at sites in China with DXA capability only)
- Randomization
- Fasting blood sample for 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
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBeAg, HBeAb, HBsAg and reflex HBsAb), HBV genotyping (A-H), virology (resistance surveillance), serum and plasma for storage, IL28B genotype, and vitamin D assessment
- Cystatin C testing for estimated glomerular filtration rate (eGFR) by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Blood sample for Fibrotest®
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- CCI [redacted]

6.3. Treatment Assessments

6.3.1. Double Blind Visits (Including Amendment 2.1 Open Label Visits Weeks 108 through 144)

Study visits Weeks 4 – 44 and Week 56 - 88 should be completed ± 3 days of the protocol specified visit date, based on the Baseline Visit.

Study visit Week 48 should be completed 14 days of the protocol specified visit date, based on the Baseline Visit.

Study visits Weeks 96, 108, 120, and 132, and 144 should be completed ± 14 days of the protocol specified visit date, based on the Baseline Visit.

6.3.1.1. Week 4

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Fasting blood sample for bone biomarkers
- Fasting urine sample for renal biomarkers
- CCI [redacted]
- Dispense blinded study drugs
- Dose in clinic and collect single blood sample for plasma PK between 15 minutes to 4 hours post-dose (subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing and provide the single PK sample)

- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.2. Week 8

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, temperature
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- CCI [redacted]
- Dispense blinded study drugs

- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and storage

6.3.1.3. Week 12

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Fasting blood sample for bone biomarkers
- Fasting urine sample for renal biomarkers
- CCI

- Dispense blinded study drugs
- Dose in clinic and collect single plasma PK sample between 15 minutes to 4 hours post-dose (subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing and provide the single PK sample)
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, plasma PK, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.4. Weeks 16, 20, 28, 32, 40, and 44

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.5. Week 24

- Complete physical examination including, vital signs (blood pressure, pulse, respiration rate and temperature), and body weight
- DXA scan of spine and hip (within ± 14 days of the expected visit date; at sites in China with capability only)
- Review concomitant medications

- Review adverse events
- Perform study drug accountability
- Fasting blood sample for 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
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) (**substudy subjects only at select sites** - separate consent required)

6.3.1.6. Week 36

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.7. Week 48

- Complete physical exam including, 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 (within 14 days of the expected visit date; at sites in China with capability only)
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Fasting blood sample for 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
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), plasma PK, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Blood sample for Fibrotest®
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) (**substudy subjects only at select sites** - separate consent required)

6.3.1.8. Weeks 56 and 88

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

- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.9. Weeks 64, 80, 108, and 132

- Symptom directed physical exam
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events
- Retrieve study drug and perform study drug accountability
- Dispense blinded study drugs (subjects already assigned to open-label TAF 25 mg QD at Week 96 per Protocol Amendment 2.1 will be dispensed open-label TAF at all subsequent visits)
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage

6.3.1.10. Week 72

- Complete physical exam including, vital signs (blood pressure, pulse, respiration rate and temperature), and body weight
- DXA scan of spine and hip (within ± 14 days of the expected visit date; at sites in China with capability only)
- Review concomitant medications
- Review adverse events
- Perform study drug accountability
- Fasting blood sample for 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
- Dispense blinded study drugs
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) (CCI [redacted]

6.3.1.11. Weeks 96 and 120

- Complete physical exam including, 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) [Week 96 only]
- Hepatic ultrasound for surveillance of hepatocellular carcinoma
- DXA scan of spine and hip to be performed (within ± 14 days of the expected visit date; at sites in China with capability only)

- Review concomitant medications
- Review adverse events
- Retrieve study drug and perform study drug accountability
- Dispense blinded study drugs (For Week 120, subjects already assigned to open-label TAF 25 mg QD at Week 96 per Protocol Amendment 2.1 will be dispensed open-label TAF)
- Fasting blood sample for 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
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Blood sample for Fibrotest® [Week 96 only]
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) CCI [redacted] [Week 96 only]

6.3.1.12. Week 144

- Complete physical exam including, 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 Week 144 visit date; at sites in China with capability only)
- Hepatic ultrasound for surveillance of hepatocellular carcinoma
- Review concomitant medications
- Review adverse events

- Retrieve study drug and perform study drug accountability
- Dispense open label TAF
- Fasting blood sample for 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
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), virology (resistance surveillance), and serum and plasma for storage
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Blood sample for Fibrotest®
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage
- Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) CCI [redacted]
  - At ED visit, ophthalmologic assessment should be performed only if not done within the last 12 weeks

6.3.2. Open Label Visits

Study visits Weeks 168 through 384/ED should be completed ± 28 days of the protocol specified visit date, based on the Baseline Visit.

6.3.2.1. Weeks 168, 216, 264, 312, and 360

- Symptom directed physical exam
- Hepatic ultrasound for surveillance of hepatocellular carcinoma
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- Review concomitant medications
- Review adverse events

- Perform open-label study drug accountability
- Dispense open-label TAF
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAg and reflex HBsAb), virology (resistance surveillance), and serum and plasma for storage. For China only, the serum and plasma samples for storage are not being collected.
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage. For China only, the urine sample for storage is not being collected.

6.3.2.2. Weeks 192, 240, 288, 336, and 384/ED

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

- Symptom directed physical exam (**At Week 240 and 384/ED,** a complete physical exam should be performed)
- Hepatic ultrasound for surveillance of hepatocellular carcinoma

  At ED visit, Hepatic ultrasound should be performed only if not done within the prior 24 weeks
- Body weight
- Vital signs: blood pressure, pulse, respiration rate, and temperature
- 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 ±28 days of the expected visit date; at sites in China with DXA capability only)

  At ED visit, DXA scan should be performed only if not done within the prior 24 weeks
- Review concomitant medications
- Review adverse events
- Retrieve study drug and perform study drug accountability

- Dispense Open Label TAF (no study drug will be dispensed at Week 384/ ED visit)
- Fasting blood sample for 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
- Blood sample for serum chemistry and liver function tests, hematology, plasma HBV DNA, serum HBsAg (quantitative), HBV serology (HBsAb and reflex HBsAg), and virology (resistance surveillance), and serum and plasma for storage. For China only, the serum and plasma samples for storage are not being collected.
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Blood sample for Fibrotest®
- Urine sample for urinalysis, pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done), and for storage. For China only, the urine sample for storage is not being collected.
- **For ED visit prior to Week 144 only, if not performed within the prior 24 weeks:** Ophthalmologic assessment, including fundoscopic examination with slit lamp and retinal photographs (both eyes) (**substudy subjects only at select sites** - separate consent required)

6.4. Post-treatment Assessments

6.4.1. HBsAg Loss and Seroconversion Subjects

Subjects who discontinue study drug due to HBsAg loss with confirmed seroconversion to anti-HBs on or after the Week 48 visit, will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 384/ED (excluding drug dispensation and accountability).

6.4.2. All other subjects who discontinue study drug

Subjects 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 alternative, commercially available HBV therapy, whichever occurs first.

6.4.3. Follow up visit assessments (all subjects)

Treatment-free Follow Up Visits should be completed ±7 days from the protocol-specified visit date, determined by the date the subject discontinued the study drug.

- 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, serum for storage, HBV serology (HBsAg and reflex HBsAb at Follow Up visits Weeks 12 and 24), and serum HBsAg (quantitative). For China only, the serum sample for storage is not being collected.
- Estimated creatinine clearance (using the Cockcroft-Gault method)
- Urine sample for urinalysis

6.5. Early Discontinuation (ED) from Study

If a subject discontinues study medication dosing for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs (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 visits and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. Early Discontinuation Assessments are described in Section 6.3.2.2.

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
- 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
- Subjects with confirmed creatinine clearance of < 30 mL/min at any time during the study will have their study drug permanently discontinued
- Lack of efficacy (virologic failure)
- 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 48 are not permitted to discontinue study drug prior to the Week 48 visit

- Discontinuation of study drug for subjects 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
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 6
- Discontinuation of the study at the request of Gilead Sciences, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

6.9. Resistance Surveillance

Genotypic sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) for resistance mutations will be conducted at Baseline for all subjects, and attempted for all viremic subjects (HBV DNA ≥ 69 IU/mL) at Week 48 and every 48 weeks until Week 384/ED visit.

At Baseline, resistance surveillance will be conducted by INNO-LiPA Multi-DR v3 (Innogenetics), which will determine the presence of HBV pol/RT mutations known to confer resistance to lamivudine, adefovir, entecavir, clevudine and/or telbivudine.

Every 48 weeks post Baseline (if viremic), resistance surveillance will be conducted by population sequencing of the HBV pol/RT.

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 virology sample for potential resistance surveillance will be collected at each study visit.

6.10. Hepatic Ultrasound for Hepatocellular Carcinoma Surveillance

Subjects will undergo hepatic ultrasound assessments for HCC surveillance, beginning at Week 96, at 24 week intervals. Subjects who have completed the Week 96 visit (under Amendment 2.1) should begin ultrasound assessments at the next visit at which an ultrasound assessment is included (see Appendix 2 and Section 6 of the Protocol).

6.11. End of Study

The end of this study will be the last subject's last observation (or visit).

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 are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., 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 (e.g., 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 (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigators 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 sub-investigator 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 (e.g., 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 (e.g., 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 5). 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 7.2.

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

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 serious adverse events (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 4-weeks after last administration of study IMP. AEs must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the AE 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 occur 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 Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed. Any SAEs and deaths, regardless of causality, that occur during the post treatment follow-up period or within 30 days of the last dose of study drug, when subject transitions to alternative, commercially available HBV therapy, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up 30-day 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 PVE.

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

- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form, but sites will transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing or emailing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PVE or to the designated CRO.

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 PVE 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 as described above.

- 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.

Safety:

North America – PRA
Email: CHOsafety@praintl.com, Fax: 1-888-772-6919

Europe (including Russian Federation), Asia Pacific – PRA
Email: MHGSafety@PRAIntl.com, Fax: +49-621-878-2181

India – PPD
Email: safetyreporting@klinera.com, Fax: +91-22-25004588

China, Vietnam – IQVIA
Email: PhV_Gilead@quintiles.com
Fax: +65 6722 5011

Japan – CMIC
Email: GPV_GileadHB@cmic.co.jp
Fax: +81-3-3493-5523

Medical Monitor:

North America – PRA
Tel: 1.866.326.5053(toll-free)
Tel: 1.434.951.4082 (direct)
Fax: 1.800.280.7035 (toll-free)
Fax: 1.913.307.5751 (direct)
Email: Gilead320-08@prahs.com

Europe (including Russian Federation), Asia Pacific – PRA
Phone: +44 179 252 5608
Fax: +49 621 878 2181
Email: MedicEU@PRAIntl.com

India – PPD
PPD
Phone: PPD
Fax: +PPD
Email: PPD

China, Vietnam – IQVIA
PPD
Phone: PPD
Mobile: PPD
Fax: PPD
Email: PPD

Japan – CMIC
PPD
Phone: PPD
Email: PPD

- 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. 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 4.

- 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 5).

- 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. Management of Potential Nephrotoxicity

Creatinine clearance (CL_{Cr}), estimated according to the Cockcroft-Gault formula, will be followed post-baseline during the study. All subjects with estimated CL_{Cr} < 50 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, Cystatin C will also be measured and the estimated glomerular filtration rate (eGFR) by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement of this parameter. During the double-blind period, any subject, who has a confirmed CL_{Cr} estimated by the Cockroft-Gault formula < 50 mL/min and also experiences a > 20% reduction in eGFR by CKD-EPI (cystatin C) from baseline, will be managed as described below:

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

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

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.

Subjects meeting the above eGFR criteria (i.e. confirmed CL_{Cr} < 50 mL/min by Cockcroft-Gault equation and > 20% reduction from baseline in eGFR by CKD-EPI equation) will be managed as follows:

- If the CL_{Cr} is confirmed to be ≥ 30 mL/min and < 50 mL/min, the subject will be required to undergo dose modification to every other day dosing of study drug during the double blind period only.
- If the CL_{Cr} is confirmed ≥ 30 mL/min to < 50 mL/min and the subject has undergone dose modification to every other day dosing of study drug and subsequently develops a confirmed CL_{Cr} ≥ 50 mL/min, the subject may revert to once daily dosing of study drug after discussion with the Gilead Medical Monitor.
- If the CL_{Cr} is confirmed to be < 30 mL/min at any time during the study, the subject will be required to permanently discontinue study drug.

- All subjects 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 two weeks of receipt of results. The following management will be required dependent upon the corresponding creatinine clearance value:

  — If creatinine clearance is < 50 ml/min, or the subject has other clinical and/or laboratory evidence of acute renal failure, the subject will be managed according to the guidance described above.

  — If creatinine clearance is ≥ 50 ml/min and the repeat testing of serum creatinine confirms a Grade 1 or Grade 2 serum creatinine elevation, it is recommended that subject be monitored weekly until the serum creatinine level returns to a value within the normal laboratory range.

- All subjects with negative or trace proteinuria at baseline that develop ≥ 1+ proteinuria on urinalysis must have a urinalysis repeated, with a concurrent urinalysis and urine chemistry, within two weeks of receipt of results. 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.

7.5.6. 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

7.5.6.1. 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.

7.5.6.2. 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, 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.

7.5.7. Management of Potential Posterior Uveitis Cases

In a nine-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12-18mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation; this finding did not occur in animals given lower doses and it has not occurred in other animal studies. This pre-clinical finding has also not been observed in humans where the dose administered is lower than that given in the dog study, nor have there been reports of posterior uveitis in human clinical studies thus far. Nonetheless, if any subject develops signs or symptoms of posterior uveitis, investigators should contact the Gilead Medical Monitor to discuss the need for additional ophthalmologic evaluation including dilated fundoscopy and optical coherence tomography (OCT).

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, lack of effect reports and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

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 or 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).

Lack of effect is defined as a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on the individual in a defined population with a given medical problem, under ideal conditions of use.

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

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 PVE 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 (e.g., 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 PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to the CRO Safety Dept. 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 PVE. Gilead PVE contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Refer to Appendix 6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

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 the CRO Safety Dept within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP, but do not apply to 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 7.3 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 study are:

- To compare the efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment-naïve and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL.

- To compare the safety and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Week 48 in treatment-naïve and treatment-experienced subjects

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

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the percent change from baseline in hip and spine BMD at Week 48

- To compare the safety of TAF 25 mg QD versus TDF 300 mg QD as determined by the change from baseline in serum creatinine at Week 48

Other secondary objectives of this study are as follows:

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL at Weeks 96, and 144

- To compare the efficacy of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B in regard to the proportion of subjects with plasma HBV DNA levels below 29 IU/mL (target not detected) at Weeks 48, 96, and 144

- To compare the biochemical (ALT normalization) response of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the serological response (loss of HBsAg with seroconversion to anti-HBs) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the change in fibrosis as assessed by FibroTest® of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B at Weeks 48, 96, and 144

- To compare the incidence of drug resistant mutations of TAF 25 mg QD versus TDF 300 mg QD at Weeks 48, 96, and 144

- To compare the change from baseline in ophthalmologic findings by fundoscopic examination of TAF 25 mg QD versus TDF 300 mg QD at Weeks 24, 48, 72, 96, and 144 in a subset of subjects

- To characterize the pharmacokinetics of TAF and tenofovir (TFV) and determine intracellular concentrations of tenofovir diphosphate (TFV-DP) within peripheral blood mononuclear cells (PBMC) in a subset of subjects receiving TAF or TDF

- To evaluate the comparative open-label efficacy, safety, and incidence of drug resistance mutations of TAF 25 mg QD from Week 144 through Week 384 in subjects initially randomized to TAF 25 mg QD and in subjects sequentially treated with TDF 300 mg QD and then switched to open-label TAF

8.1.2. Primary Endpoint

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

8.1.3. Secondary Endpoints

The key secondary safety endpoints are:

- The percent change from baseline at Week 48 in hip BMD

- The percent change from baseline at Week 48 in spine BMD

- The change from baseline at Week 48 in serum creatinine

8.1.4. Other Endpoints of Interest

- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Weeks 96 and 144

- The proportion of subjects with plasma HBV DNA < 29 IU/mL (target not detected) at Weeks 48, 96, and 144

- The proportion of subjects with ALT normalization (by central laboratory and AASLD criteria) at Weeks 48, 96, and 144

- The proportion of subjects with HBsAg loss at Weeks 48, 96, 144, 240, and 384

- The proportion of subjects with HBsAg seroconversion to anti-HBs at Weeks 48, 96, 144, 240, and 384
- The change from baseline in fibrosis as assessed by FibroTest® at Weeks 48, 96, 144, 240 and 384
- The incidence of drug resistant mutations at Weeks 48, 96, 144, 240, and 384
- The change from baseline in ophthalmologic findings by fundoscopic examination at Weeks 24, 48, 72, 96, and 144 in a subset of subjects
- The proportion of subjects with treatment-emergent proteinuria (by dipstick) at Weeks 48, 96, 144, 240, and 384

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis the Full Analysis Set (FAS), defined as all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the randomized treatment assignment.

8.2.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set (SAS), defined as all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment actually received.

All data collected during treatment will be included in the safety summaries. Data collected during treatment free follow up will be summarized or listed separately.

8.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are randomized and have received at least one dose of study medication and for whom concentration data of any analytes of interest (eg, TAF and TFV) are available. The PK analysis set will be used for analyses of general pharmacokinetics.

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8.2.1.4. Biomarkers

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

8.2.2. Data Handling Conventions

For the primary endpoint missing data will be handled using a missing = failure approach, unless otherwise specified.

For key secondary safety endpoints, missing data will be handled via a Last Observation Carried Forward (LOCF) method.

For other categorical secondary efficacy endpoints, missing data will be handled using a missing = failure approach. For the drug resistant mutations endpoint, a missing = excluded approach will be employed.

Sensitivity analyses will be performed as warranted.

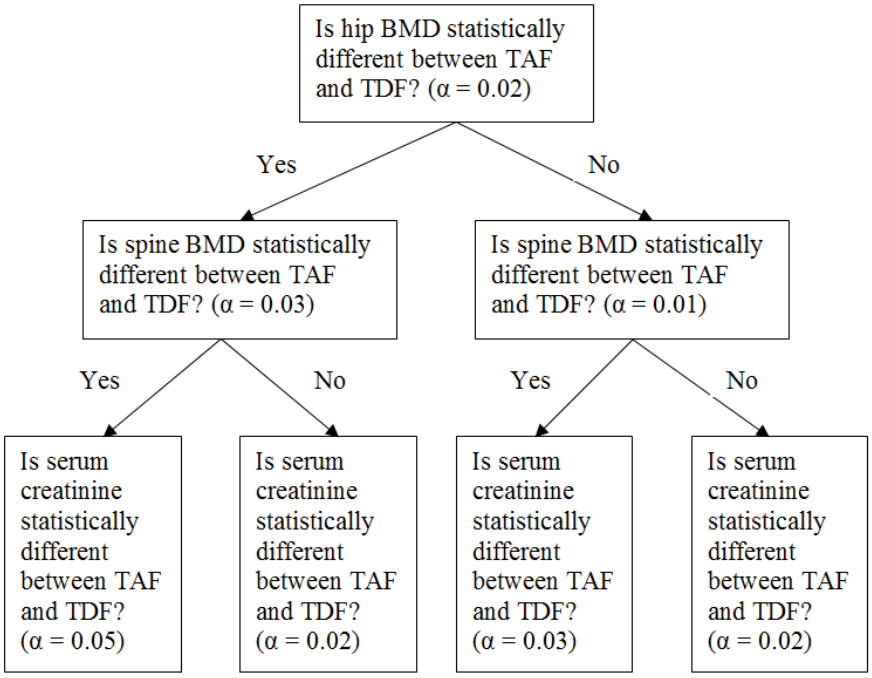
8.3. Multiplicity Adjustments

The primary hypothesis of non-inferiority between TAF 25 mg QD and TDF 300 mg QD with respect to the proportion of subjects with HBV DNA < 29 IU/mL will be tested first. If non-inferiority is established, then multiplicity adjustments will be performed for the secondary endpoints with a fallback procedure using the following weights:

a) Hip BMD (weight = 0.4)

b) Spine BMD (weight = 0.2)

c) Serum creatinine (weight = 0.4)



8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group and overall.

Demographic summaries will include sex, race/ethnicity, geographical region, randomization stratification group, and age.

Baseline data will include a summary of body weight, height, body mass index, $\log_{10}$ HBV DNA level, years positive for HBV, ALT level (≤ ULN, > ULN), previous oral nucleoside/nucleotide treatment experience, previous interferon experience, and genotype.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy analysis will be conducted when approximately 390 randomized subjects complete 48 weeks of the double-blind treatment period or discontinue prematurely. A two-sided 95% confidence interval, based on the large sample theory adjusted for the randomization stratification factors (the adjusted Mantel-Haenszel proportions), for the difference (TAF – TDF) in the proportion of subjects who achieved HBV DNA < 29 IU/mL will be used to compare the treatment groups. A non-inferiority will be declared if the lower bound of this confidence interval exceeds a non-inferiority margin of –0.10. If non-inferiority is established, the lower bound of the 95% CI will be compared to 0; if the lower bound of the 95% CI is greater than 0, then superiority of TAF over TDF will be established using the same confidence interval. Details will be provided in the statistical analysis plan.

8.5.1.1. Justification of the non-inferiority margin

At Week 48 in study GS-US-174-0102, the proportion of subjects with HBV DNA < 29 IU/mL in the TDF arm was 91.2%. At Week 48 in study GS-98-438, the proportion of subjects with HBV DNA < 29 IU/mL in the placebo was 0%. The non-inferiority margin of 10% would preserve more than 88% of the lower bound of the 95% confidence interval of the difference between TDF and placebo.

	N_{TDF}	N_{PBO}	Response rate in TDF	Response rate in PBO	Difference	95% confidence interval lower bound
	250	61	91.2%	0%	91.2%	87.7%
Preserve at least 88% of lower bound						10%

Furthermore, at Week 48 in study GS-US-174-0102, the proportion of subjects with HBV DNA < 29 IU/mL in the TDF arm was 91.2% and the proportion of subjects with HBV DNA < 29 IU/mL in adefovir (ADV) arm was 56.0%. The non-inferiority margin of 10% would preserve more than 60% of the lower bound of the 95% confidence interval of the difference between TDF and adefovir (ADV).

	N_{TDF}	N_{ADV}	Response rate in TDF	Response rate in ADV	Difference	95% confidence interval lower bound
Study 174-0102	250	125	91.2%	56.0%	35.2%	25.8%
Preserve at least 60% of lower bound						10%

8.5.2. Analyses of Other Endpoints of Interest

Continuous secondary endpoints will be summarized using conventional descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group and overall. A Wilcoxon rank sum test will be used to compare the treatment groups, in an exploratory manner.

Categorical secondary endpoints will be summarized by number and percentage of subjects that meet the endpoint. A two-sided Mantel-Haenszel test, controlling for the randomization strata, will be used to compare the treatment groups, in an exploratory manner. Missing data will be handled by the missing = failure approach.

For the incidence of drug resistant mutations, the missing = excluded approach will be employed.

An analysis of the China subpopulation will also be conducted when approximately 150 randomized and treated China subjects complete 48 weeks of double-blind treatment or discontinue prematurely to examine the consistency of the responses between the China subpopulation and the overall population.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose will be summarized by treatment group (according to the drug received). Data for the pretreatment and treatment-free follow-up periods will be included in data listings.

8.6.1. Key Secondary Safety Analyses

The percent change from baseline in hip and spine BMD at Week 48 will be analyzed using an ANOVA model. The model will include treatment group as fixed effect. The details are provided in the Statistical Analysis Plan (SAP).

The change from baseline in serum creatinine at Week 48 will be analyzed using an ANCOVA model with baseline serum creatinine as a covariate, and treatment group as a fixed effect. The details are provided in the SAP.

8.6.2. Extent of Exposure

A subject's extent of exposure to drug data will be generated from the drug administration data. Exposure data will be summarized by treatment group.

8.6.3. 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 treatment up to the date of last dose of treatment. 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 by treatment group:

- 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

8.6.4. 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 5.

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 and including the date of last dose of treatment, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

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

8.7. Pharmacokinetic Analysis

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

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8.7.1. Biomarker Analysis

Selected bone biomarkers, including C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP), and selected renal biomarkers, including urine retinol binding protein, and urine beta-2-microglobulin, will be summarized by treatment group and visit using descriptive statistics. The difference in change from baseline in these biomarkers between two treatment arms will be tested using Wilcoxon rank sum test.

8.8. Sample Size

With respect to the primary efficacy endpoint, a sample size of 130 for the TDF 300 mg group and 260 for the TAF 25 mg group will have 90% power to rule out the non-inferiority margin of 10% at a one-sided significance level of 0.025. This assumes a rate of 91% in the TDF 300 mg group and 91% in the TAF 25 mg group in the proportion of subjects with HBV DNA < 29 IU/mL. A similar response rate in the TDF group was observed in GS-US-174-0102 {Marcellin 2007, Marcellin 2008}.

This sample size (n=260 for the TAF 25 mg arm, n=130 for the TDF 300 mg arm) also provides at least 90% power to detect a 1% difference in the percentage change from baseline in hip BMD at Week 48 (assuming a 1.17% change from baseline in TDF 300 mg arm and 0.17% change from baseline in the TAF 25 mg arm, with a common standard deviation of 2.20% and a two-sided $\alpha = 0.025$); a 77% power to detect a 1% difference in the percentage change from baseline in spine BMD at Week 48 (assuming a 1.69% change from baseline in the TDF 300 mg arm and 0.69% change in the TAF 25 mg arm, with a common standard deviation of 3.08% and a two-sided $\alpha = 0.025$); a 52% power to detect a 0.03 mg/dL difference in the change from baseline in serum creatinine at Week 48 (assuming a 0.04 mg/dL change from baseline in the TDF 300 mg arm and 0.01 mg/dL change from baseline in the TAF 25 mg arm, with a

common standard deviation of 0.12). These assumptions were derived from studies GS-98-437, GS-98-438, GS-US-174-0102, GS-US-174-0103, and GS-US-174-0121.

For China, approximately 150 additional subjects (100 subjects TAF 25 mg QD and matched placebo of TDF 300 mg QD, and 50 subjects TDF 300 mg QD and matched placebo of TAF 25 mg QD) will be enrolled.

8.9. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design

The DMC will convene approximately every 24 weeks following the time of randomization of the first subject during the blinded portion of the protocol and approximately every 48 weeks during the open-label period.

The DMC's specific activities will be defined by a mutually agreed upon charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

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 (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), 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 sub-investigators 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 sub-investigator's) participation in the study. The investigator and sub-investigator 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) 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. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC *a*ny modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC 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- or IEC-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 or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

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 or IEC, or laboratory. Laboratory specimens must be labeled in such as way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions.
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, IRB or IEC 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, ie, 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. 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

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used (empty kits and/or bottles) 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. 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 QA, 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 IRBs or IECs, 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 or IEC in accordance with local requirements and receive documented IRB or IEC 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. 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.

9.3.2. 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.

9.3.3. 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.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B

GS-US-320-0108, Amendment 3.4, 25 September 2019

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

PPD

PPD

PPD

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

	Screening (45 days)	BL	Week																				
			4	8	12	16	20	24	28	32	36	40	44	48[a]	56	64	72	80	88	96[a,e]	108 132[e]	120	144[e]
	Visit Window		± 3 days											-14 days	±3 days					± 14 days			
Informed Consent	X																						
Review of Inclusion/ Exclusion Criteria	X	X																					
Medical History, including HBV history	X																						
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination including vital signs, and weight	X	X						X						X			X			X		X	X
Height	X																						
Symptom-directed Physical Exam			X	X	X	X	X		X	X	X	X	X		X	X		X	X		X		
Body weight			X	X	X	X	X		X	X	X	X	X		X	X		X	X		X		
ECG[b]	X													X						X			X
Vital Signs[c]			X	X	X	X	X		X	X	X	X	X		X	X		X	X		X		
Randomization		X																					
DXA[d] (spine & hip)	X							X						X			X			X		X	X
Fracture Risk Assessment[q]		X																					
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensed/Retrieved[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing in-clinic[f]			X		X																		

	Screening (45 days)	BL	Week																				
			4	8	12	16	20	24	28	32	36	40	44	48[a]	56	64	72	80	88	96[a,e]	108 132[e]	120	144[e]
	Visit Window		± 3 days											-14 days	±3 days					± 14 days			
Serum Chemistry and Liver Function Tests[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Estimated Creatinine Clearance (by Cockcroft-Gault Method)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cystatin C (for estimated eGFR)		X																					
Plasma HBV DNA Levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum HBsAg (quantitative)	X	X			X			X			X			X		X		X		X	X	X	X
HBV Serology[h]	X	X			X			X			X			X		X		X		X	X	X	X
HBV Genotyping (A-H)		X																					
Virology (resistance surveillance)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1, HDV, HCV	X																						
α-fetoprotein	X																						
Fibrotest®		X												X						X			X
IL28B Genotype		X																					
Vitamin D		X																					
Plasma PK			X	X	X	X	X	X	X	X	X	X	X	X									
Fasting Blood for Bone Biomarkers[i]		X	X		X			X						X			X			X		X	X
Fasting Urine for Renal Biomarkers[i]		X	X		X			X						X			X			X		X	X
Fasting Metabolic Panel[j]		X						X						X			X			X		X	X
Serum Pregnancy Test[k]	X																						

	Screening (45 days)	BL	Week																			
			4	8	12	16	20	24	28	32	36	40	44	48[a]	56	64	72	80	88	96[a,e]	108 132[e]	120	144[e]
	Visit Window		± 3 days											-14 days	±3 days					± 14 days			
Urine Pregnancy Test[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI	CCI																						
CCI																							
CCI																							
Urine for Storage		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																							
Hepatic Ultrasound[r]																				X		X	X
CCI																							

	Week										
	168	**192**	**216**	**240**	**264**	**288**	**312**	**336**	**360**	**384/ED[o]**	**FU[p]**
Visit windows	**±28 days**										**±7 days**
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination including vital signs, and weight				X						X	
Symptom-directed Physical Exam	X	X	X		X	X	X	X	X		X
Body weight	X	X	X		X	X	X	X	X		X
ECG[b]		X		X		X		X		X	
Vital Signs[c]	X	X	X		X	X	X	X	X		X
DXA (spine & hip)[d]		X		X		X		X		X	
Study Drug Accountability	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensed/Retrieved[e]	X	X	X	X	X	X	X	X	X	X[e]	
Serum Chemistry and Liver Function Tests[g]	X	X	X	X	X	X	X	X	X	X	X
Est Creatinine Clearance (Cockcroft-Gault)	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X
Plasma HBV DNA Levels	X	X	X	X	X	X	X	X	X	X	X
Serum HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X
HBV Serology[h]	X	X	X	X	X	X	X	X	X	X	X
Virology (resistance surveillance)	X	X	X	X	X	X	X	X	X	X	
Fibrotest®		X		X		X		X		X	
Fasting Blood for Bone Biomarkers[i]		X		X		X		X		X	
Fasting Urine for Renal Biomarkers[i]		X		X		X		X		X	
Fasting Metabolic Panel[j]		X		X		X		X		X	
Urine Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	

	Week										
	168	192	216	240	264	288	312	336	360	384/ED[o]	FU[p]
Visit windows	±28 days										±7 days
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Serum and plasma for storage[s]	X	X	X	X	X	X	X	X	X	X	X (serum only)
Urine for Storage[s]	X	X	X	X	X	X	X	X	X	X	
CCI											
Hepatic Ultrasound[r]	X	X	X	X	X	X	X	X	X	X	

a The visit window for Week 48 visit is 14 days. The visit window for Week 96 is ±14 days.
b Subjects must rest quietly in the supine position for a minimum of 5 minutes prior to the recording
c Vital signs include blood pressure, pulse, respiration rate, and temperature
d DXA scans will be performed only at sites in China with capability. The initial (baseline) DXA will be performed during Screening and should be completed at least 14 days prior to the first dose of study drug. The Week 48 DXA window is 14 days only. DXA is required for Early Discontinuation (ED) visit if not done within the last 24 weeks.
e Subjects already assigned to open-label TAF 25 mg QD per Amend 2.1 continue on open-label TAF 25 mg QD. Otherwise, blinded study drug will be dispensed until Week 144 visit. Open label TAF will be dispensed from Week 144 through Week 360. At Week 384/ED, study drug will not be dispensed
f It is preferred that subjects take their study drug according to a morning dosing schedule; subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing and provide the single PK sample being collected at Week 4 and 12 visits.
g 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 through Week 96, and then at Weeks 120, 144, and then every 48 weeks through Week 384/ED. At Baseline, Weeks 24, 48, 72, 96, 120, 144, 192, 240, 288, 336 and 384/ED, subject will be fasting for serum and glucose and metabolic panel. Coagulation panel will be done at Screening and then as a reflex only test for ALT flares.
h HBeAg and HBeAb will be done at Screening and Baseline visits. HBsAg and reflex HBsAb will be done at Screening and Baseline visits, and every 12 to 16 weeks until week 144, every 24 weeks untile Week 384/ED and at Follow Up visits Weeks 12 and 24.
i Blood for selected bone biomarkers and urine for selected renal biomarkers will be collected in a fasted state. Required for ED visit if the last sample was collected >24 weeks prior
j Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides).
k For female subjects of childbearing potential. In the event of a positive urine test, a serum pregnancy test will be done
l CCI
m CCI

n CCI [redacted].

o The Early Discontinuation (ED) visit should be performed within 72 hours of the last study drug dose (+ 3 days)

p Subjects who discontinue study drug for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs will be followed every 4 weeks for 24 weeks or up to initiation of alternative, commercially available HBV therapy, whichever occurs first. Subjects who lose HBsAg with confirmed seroconversion to anti-HBs should discontinue study drug within 3-6 months following confirmation of HBsAg loss and seroconversion to anti-HBs or after Week 48, if seroconversion occurs prior to this visit. These subjects will be followed off treatment every 4 weeks for 12 weeks and then per the study visit schedule through Week 384/ED.

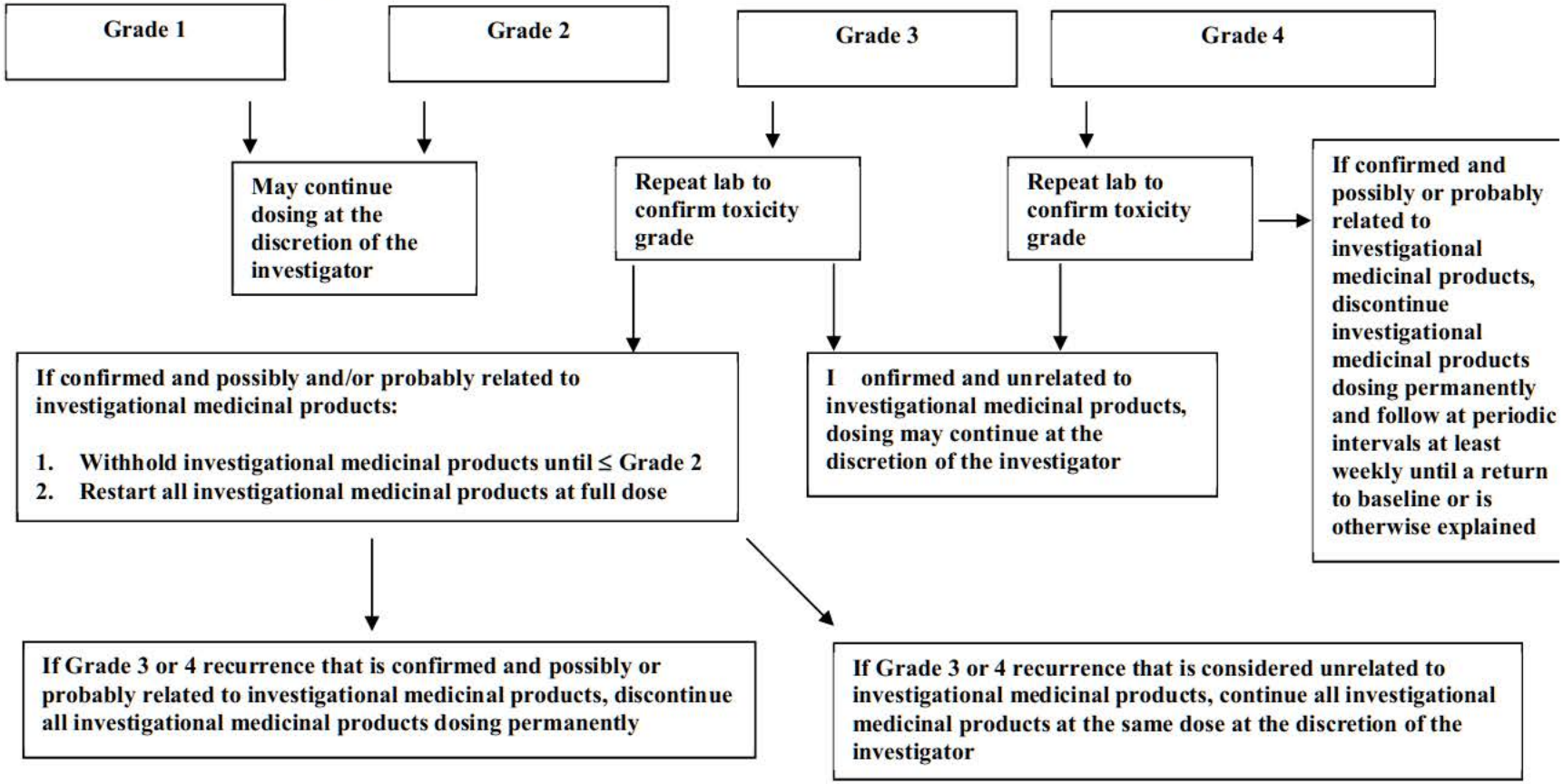
q Complete the Fracture Risk Assessment specific eCRF at sites in China with DXA capability only.

r Hepatic ultrasound for HCC surveillance

s CCI [redacted]


CCI

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	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
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/ μL	200 to < 300/mm^3 200 to < 300/ μL	100 to < 200/mm^3 100 to < 200/ μL	< 100/mm^3 < 100/ μL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100.0 to < 125.0 GI/L	50,000 to < 100,000/mm^3 50.0 to < 100.0 GI/L	25,000 to < 50,000/mm^3 25.0 to < 50.0 GI/L	< 25,000/mm^3 < 25.0 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.0 GI/L to 2.5 GI/L	1,500 to < 2,000/mm^3 1.5 to < 2.0 GI/L	1000 to < 1,500/mm^3 1.0 to < 1.5 GI/L	< 1000/mm^3 < 1.0 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	— —	— —

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric** **≥ 7 Days**	> 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
Hypophosphatemia **Adult and Pediatric** **> 14 Years**	2.0 mg/dL to < LLN 0.63 mmol/L to < LLN	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol /L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol /L	> 30.0 mg/dL > 513 µmol /L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol /L	> 25.0 mg/dL > 428 µmol /L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	> ULN to 10.0 mg/dL > ULN to 597 µmol /L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol /L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol /L	> 15.0 mg/dL > 895 µmol /L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol /L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol /L	0.5 to < 1.0 mg/dL 27 to < 57 µmol /L	< 0.5 mg/dL < 27 µmol /L
Creatinine	> 1.50 to 2.0 mg/dL > 133 to 177 µmol /L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol /L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol /L	> 6.00 mg/dL > 530 µmol /L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L > 190 mg/dL >4.92 mmol/L	NA NA

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

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

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

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

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

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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g., 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, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., 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

RESPIRATION				
	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 Respiration 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	Respiration failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiration 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%	Respiration 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 [e.g., tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., 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 (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., 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 (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (e.g., 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 (e.g., 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 Respiration 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 (e.g., status epilepticus), or difficult to control (e.g., 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 (e.g., severity or focality)	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

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

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., 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 (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., myxedema coma)
Lipoatrophy (e.g., 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 (e.g., 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 antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial 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 (e.g., 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 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with study drug have not been evaluated. If females are using hormonal agents for contraception, the safety and/or efficacy may be affected by possible drug-drug interaction. However, it is recommended that the hormonal agent be continued and that a non-hormonal method(s) be used concurrently. If females utilize hormonal agents as one of their contraceptive methods, it is required that the same hormonal method be used for at least 3 months before study dosing. Please refer to the latest version of the Investigator's Brochure for GS-7340 for additional information

2. Definition of Female of Childbearing Potential

- For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a pubertal female who has not yet started menstruating. A woman who has had a tubal sterilization is considered to be of childbearing potential.
- A female subject ≤ 54 years in age, with the absence of normal menses is considered to be of childbearing potential. Exceptions must be discussed with the medical monitor.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed)
- Age > 54 years, with the cessation (for ≥ 12 months) of previously occurring menses due to ovarian failure, will not be considered to be childbearing potential.

3. Contraceptive Requirements for Female Subjects

Female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening visit throughout the study period and for 30 days following the last dose of study drug. Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while participating in the study. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; (2) two barrier methods where one method is the male condom; or (3) use of an intrauterine device (IUD) or tubal sterilization; see Appendix Table 1 below; or (4) complete abstinence from intercourse. Periodic abstinence from intercourse (e.g. calendar, ovulation, sumptothermal, post-ovulation methods) is not permitted.

Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1) prior to receiving the first dose of study drug. Lactating females must discontinue nursing before IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(use both OR choose one and use with a hormone method)</th></tr>
<tr><td rowspan="2">Intrauterine Devices (IUDs)
• Copper T 380A IUD
• LNg 20 IUD

Tubal Sterilization</td><td>Estrogen and Progesterone
• Oral contraceptives
• Transdermal patch
• Vaginal ring
Progesterone
• Injection
• Implant</td><td>• Diaphragm with spermicide
OR
• Cervical cap with spermicide
• Male condom (with or without spermicide)</td></tr>
<tr><td colspan="2">Partner's vasectomy must be used with a hormone or barrier method.</td></tr>
</table>

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

4. Contraceptive Requirements for Male Subjects

Male subjects must agree to use protocol specified method of contraception during heterosexual intercourse and avoid sperm donation from the time of the first dose of study drug and throughout the study period, and for at least 30 days after administration of the last dose of study medication

Use of condoms, except for lambskin, has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

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.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.6.2.1.