FINAL WEEK 384 CLINICAL STUDY REPORT

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-Positive, Chronic Hepatitis B
Name of Test Drug:	Tenofovir Alafenamide
Dose and Formulation:	Tenofovir Alafenamide 25-mg tablet
Indication:	Chronic Hepatitis B
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-320-0110
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	115561 2013-000636-10
ClinicalTrials.gov Identifier:	NCT01940471
Study Start Date:	11 September 2013 (first participant screened)
Study End Date:	13 October 2022 (last participant last visit for this report)
Principal or Coordinating Investigator:	Name: PPD Affiliation: Asan Medical Center 88, Olympic-ro 43-gil Songpa-gu, Seoul, 05505 South Korea
Sponsor Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	07 March 2023

Previous Report Date(s):	28 February 2018 (Interim Week 144 clinical study report [CSR]) 02 February 2017 (Interim Week 96 CSR) 27 September 2016 (Interim Week 48 CSR Erratum 1) 21 December 2015 (Interim Week 48 CSR)

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-320-0110
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

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-Positive, Chronic Hepatitis B

Investigators: This is a multicenter study.

Study Centers: Participants were enrolled in a total of 161 sites: 12 in Australia, 4 in Bulgaria, 12 in Canada, 4 in France, 5 in Hong Kong, 18 in India, 7 in Italy, 16 in Japan, 2 in New Zealand, 5 in Poland, 5 in Romania, 12 in Russia, 3 in Singapore, 2 in Spain, 22 in South Korea, 8 in Taiwan, 5 in Turkey, 4 in the United Kingdom, and 15 in the United States.

These enrollment numbers do not include participants who were enrolled in mainland China (hereafter referred to as China). This clinical study report (CSR) does not include any data from the cohort of participants in China.

Publications:

Chan HLY, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1:185-95

Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018;68 (4):672-81

Cathcart AL, Chan HLY, Bhardwaj N, Liu Y, Marcellin P, No Resistance to Tenofovir Alafenamide Detected through 96 Weeks of Treatment in Patients with Chronic Hepatitis B Infection. Antimicrob Agents Chemother 2018; Sep 24;62(10):e01064-18

Seto WK, Asahina Y, Brown TT, Peng CY, Stanciu C, Abdurakhmanov D. Improved Bone Safety of Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate Over 2 Years in Patients with Chronic HBV Infection. Clin Gastroenterol Hepatol. 2018 Jun 20:S1542-3565(18)30633-5

Chang S, Hedskog C, Parhy B, Martin R, Mo H, Miorova E, et al. Sequence Characterization of Extracellular HBV RNA in Patient Plasma. Journal of Viral Hepatitis; 2022 October

Pan CQ, Chang TT, Bae SH, Brunetto M, Seto WK, Coffin CS, et al. Antiviral Kinetics of Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate over 24 Weeks in Women of Childbearing Potential with Chronic HBV. PLoS One; 2021 May

Liu Y, May L, Liu X, Martin R, Svarovskaia E, Gaggar A, et al. Developing a sensitive HBV genotyping assay for HBV DNA suppressed patients using both DNA and RNA sequencing. Journal of Medical Virology; 2020 March

Study Period:

11 September 2013 (first participant screened)
13 October 2022 (last participant last visit for this report)

Phase of Development: Phase 3

Objectives

The primary objectives of this study were as follows:

- To compare the efficacy of TAF 25 mg once daily (QD) versus TDF 300 QD for the treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) at Week 48 in treatment-naive and treatment-experienced participants. The primary efficacy parameter was the proportion of participants with plasma hepatitis B virus (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-positive CHB at Week 48 in treatment-naive and treatment-experienced participants

The key secondary safety objectives of this study were 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

The key secondary efficacy objective of this study was as follows:

- To compare the serological response (loss of HBeAg with seroconversion to antibody against hepatitis B e antigen [anti-HBe]) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive CHB at Week 48

Other secondary objectives of this study were as follows:

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

- To compare the biochemical (alanine aminotransferase [ALT] normalization by central laboratory and American Association for the Study of Liver Diseases [AASLD] criteria) response of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive CHB at Weeks 48, 96, and 144
- To compare the serological response (loss of HBeAg with seroconversion to anti-HBe) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive CHB at Weeks 96 and 144

- To compare the serological response (loss of hepatitis B surface antigen [HBsAg] with seroconversion to antibody against hepatitis B surface antigen [anti-HBs]) of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive CHB 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-positive CHB 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 early discontinuation [ED] visit if prior to Week 144 and more than 24 weeks since prior exam) in a subset of participants
- To characterize the pharmacokinetics (PK) of TAF and tenofovir (TFV) and determine intracellular concentrations of TFV-DP within peripheral blood mononuclear cells (PBMCs) in participants receiving TAF or TDF
- **To evaluate the comparative open-label (OL) efficacy, safety, and drug resistance mutations of TAF 25 mg QD in participants initially randomized to TAF 25 mg QD and in participants sequentially treated with TDF 300 mg QD and then switched to OL TAF 25 mg QD**

Methodology:

This was a Phase 3, randomized, double-blind (DB), noninferiority, international, multicenter study comparing the efficacy, safety, and tolerability of TAF 25 mg QD versus TDF 300 mg QD for the treatment of HBeAg-positive CHB infection in treatment-naive and treatment-experienced participants.

Participants were randomized in a 2:1 (TAF group:TDF group) ratio to 1 of the following 2 treatment groups:

- **TAF group:** TAF 25 mg QD and matched placebo of TDF 300 mg QD
- **TDF group:** TDF 300 mg QD and matched placebo of TAF 25 mg QD

Randomization was stratified by plasma HBV DNA level (≥ 8 log10 IU/mL versus < 8 log10 IU/mL) and oral antiviral (OAV) treatment status (treatment naive versus treatment experienced) at screening.

Under Protocol Amendments 1 and 2, participants who completed 96 weeks of DB treatment could begin an OL extension period to receive TAF 25 mg QD for up to an additional 48 weeks (ie, Weeks 96 through 144). Under Protocol Amendment 3, participants who completed 144 weeks of DB treatment could begin an OL extension period to receive TAF 25 mg QD for up to an additional 240 weeks (ie, Weeks 144 through 384). Participants who were consented under Protocol Amendment 3 after entering OL treatment at Week 96 continued OL treatment through Week 384. Participants who permanently discontinued study drug (either prematurely or at the end of OL phase [Week 384]) for reasons other than HBsAg loss with confirmed seroconversion to anti-HBs were followed every 4 weeks for 24 weeks off treatment (treatment-free follow-up [TFFU]) or up to the initiation of appropriate, alternative HBV therapy, whichever occurred first.

Results relating to the primary objective and the key secondary objectives are described in the interim Week 48 CSR (21 December 2015). Results relating to other secondary objectives evaluating the long-term efficacy, safety, and tolerability of treatment with TAF and TDF beyond Week 48 and on or before Week 144 are described in the Week 96 Interim CSR (02 February 2017), and Week 144 Interim CSR (28 February 2018).

This final CSR presents long-term and final study results after all participants had completed the Week 384 study visit or had prematurely discontinued study drug and a cumulative assessment of safety data in the OL phase through the end of the study. Results are also presented for participants who completed the treatment-free follow-up (TFFU) phase or prematurely discontinued the study.

Data are presented as outlined in the Statistical Methods section below. Data from the cohort of participants in China are not included.

Number of Participants (Planned and Analyzed):

Planned: 864 participants (576 in the TAF group and 288 in the TDF-TAF group)
Analyzed (by analysis set):

		TDF-TAF			
	TAF	Week 96	Week 144	Total	Overall
Participants in Randomized Analysis Set	582	133	159	293	875
Participants in Safety Analysis Set	581 (99.8%)	133 (100.0%)	159 (100.0%)	292 (99.7%)	873 (99.8%)
Participants in OL Safety Analysis Set	514 (88.3%)	114 (85.7%)	139 (87.4%)	253 (86.3%)	767 (87.7%)
Participants in Treatment-Free Follow-Up Safety Analysis Set	111 (19.1%)	26 (19.5%)	26 (16.4%)	52 (17.7%)	163 (18.6%)
Participants in Full Analysis Set (FAS)	581 (99.8%)	133 (100.0%)	159 (100.0%)	292 (99.7%)	873 (99.8%)
Participants in Treatment-Free Follow-Up Full Analysis Set	111 (19.1%)	26 (19.5%)	26 (16.4%)	52 (17.7%)	163 (18.6%)
Participants in Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion	565 (97.1%)	129 (97.0%)	156 (98.1%)	285 (97.3%)	850 (97.1%)
Participants in Treatment-Free Follow-Up Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion	59 (10.1%)	14 (10.5%)	17 (10.7%)	31 (10.6%)	90 (10.3%)
Participants in Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion	576 (99.0%)	129 (97.0%)	159 (100.0%)	288 (98.3%)	864 (98.7%)
Participants in Treatment-Free Follow-Up Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion	107 (18.4%)	25 (18.8%)	24 (15.1%)	49 (16.7%)	156 (17.8%)

Participants in Hip DXA Analysis Set	566 (97.3%)	132 (99.2%)	154 (96.9%)	286 (97.6%)	852 (97.4%)
Participants in Spine DXA Analysis Set	570 (97.9%)	132 (99.2%)	154 (96.9%)	286 (97.6%)	856 (97.8%)

DXA = dual-energy x-ray absorptiometry; HBsAg = hepatitis B surface antigen
The denominator for percentages is based on the number of participants in the Randomized Analysis Set.
One participant in the Randomized Analysis Set was randomized and never treated due to withdrawal of consent and was not included in the Week 96/144 TDF-TAF group.

Diagnosis and Main Criteria for Inclusion:

Male and nonpregnant, nonlactating female participants aged ≥ 18 years with CHB infection (ie, HBsAg positive for > 6 months) who were HBeAg positive with screening HBV DNA ≥ 2×10^4 IU/mL and screening serum ALT > 60 U/L (males) or > 38 U/L (females) and ≤ 10 × upper limit of normal (ULN) using the central laboratory criteria, were treatment naive or treatment experienced, had a normal electrocardiogram (ECG) (or if abnormal, determined by the investigator not to be clinically significant), and had an estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault ($eGFR_{CG}$) formula.

Duration of Treatment:

Under Protocol Amendments 1 and 2, treatment duration was 96 weeks of randomized, DB treatment followed by up to 48 weeks of OL extension (ie, a total of 144 weeks). Under Protocol Amendment 3, treatment duration was 144 weeks of randomized, DB treatment followed by an additional 240 weeks of OL treatment with TAF (through Week 384). Participants who were consented under Protocol Amendment 3 after entering OL treatment at Week 96 were to continue OL treatment through Week 384.

Participants who lost HBsAg with confirmed seroconversion to anti-HBs were to discontinue study drugs within 3 to 6 months following confirmation of seroconversion to anti-HBs, or after Week 48 if seroconversion occurred prior to this visit. Participants who permanently discontinued study drug due to HBsAg loss with confirmed seroconversion to anti-HBs on or after the Week 48 visit were followed every 4 weeks for 24 weeks off treatment (TFFU) and then per the original study visit schedule through Week 384/ED (excluding drug dispensation and accountability).

Test Product, Dose, Mode of Administration, and Batch No.:

TAF 25-mg tablet QD and matching placebo of TDF 300-mg tablet QD were each administered orally.

Additional TAF batch number since the GS-US-320-0110 Interim Week 144 CSR: CCKBF

Reference Therapy, Dose, Mode of Administration, and Batch No.:

TDF 300-mg tablet QD plus matching placebo of TAF 25-mg tablet QD were each administered orally.

No additional batch numbers since the Interim Week 144 CSR (28 February 2018).

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the proportion of participants with HBV DNA < 29 IU/mL at Week 48.

Secondary efficacy endpoints evaluated at Weeks 48, 96, 144, 240, and 384 included the proportion of participants with plasma HBV DNA < 29 IU/mL, HBV DNA < 29 IU/mL (target not detected), HBsAg loss and seroconversion to anti-HBs, HBeAg loss and seroconversion to anti-HBe, serum ALT normalization (by central laboratory and AASLD criteria), change from baseline in fibrosis, change from baseline in $\log_{10}$ HBV DNA (IU/mL), change from baseline in $\log_{10}$ HBsAg (IU/mL), change from baseline in ALT, and incidence of drug-resistant mutations. The incidence of drug resistant mutations will be reported in a separate virology report.

Pharmacokinetics/Pharmacodynamics:

No PK or pharmacodynamic (PD) analyses were performed for this report.

Safety:

Baseline and postbaseline safety assessments included treatment-emergent adverse events (AEs), hip and spine BMD using dual-energy x-ray absorptiometry (DXA), concomitant medications, ECG, physical examinations, vital signs, fundoscopic examination (for a subgroup of participants), and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing).

Laboratory tests also included the following fasted serum bone laboratory parameters:

- Bone resorption marker C-type collagen sequence
- Bone formation markers procollagen type 1 N-terminal propeptide, bone-specific alkaline phosphatase, and osteocalcin
- Bone metabolism marker parathyroid hormone

Renal laboratory parameters were assessed as follows:

- Serum creatinine
- Estimated glomerular filtration rate (GFR) by 3 formulas ($eGFR_{CG}$, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine [$eGFR_{CKD\text{-}EPI,\ creatinine}$] and cystatin C [$eGFR_{CKD\text{-}EPI,\ cysC}$] equations). Estimated $GFR_{CKD\text{-}EPI,\ cysC}$ was assessed at baseline only.
- Treatment-emergent proteinuria by urinalysis (dipstick) and quantitative assessment as follows:
  - Urine protein to creatinine ratio
  - Urine albumin to creatinine ratio
  - Urine retinol binding protein to creatinine ratio

— Urine beta-2-microglobulin to creatinine ratio

- Renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate, urine fractional excretion of phosphate, and urine fractional excretion of uric acid were also assessed.

Statistical Methods:

Efficacy:

The primary efficacy analysis was described in the interim Week 48 CSR. Secondary efficacy analyses for Weeks 96 and 144 were reported in the interim Week 96 and interim Week 144 CSRs, respectively.

For the Week 384 efficacy analysis, all secondary efficacy endpoints involving proportions were analyzed using the missing = failure (M = F) approach based on participants in the Full Analysis Set (FAS) (excluding participants from Site PPD who completed planned study treatment through Week 144. Site PPD did not participate in Protocol Amendment 3; therefore, participants from this site discontinued study on or before Week 144) and missing = excluded (M = E) approach based on participants in the FAS if applicable.

The change from baseline in HBV DNA (log_{10} IU/mL), HBsAg (log_{10} IU/mL), and ALT (U/L) was summarized by visit using observed data (ie, missing values were excluded).

Fibrosis assessed by FibroTest at each visit and the change from baseline in FibroTest score were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment group. A shift table of fibrosis stage based on FibroTest score from baseline, and every 48 weeks thereafter through Week 384/ED was also provided.

For participants in the TFFU FAS, only HBV DNA, ALT, HBeAg loss/seroconversion, HBsAg, and HBsAg loss/seroconversion endpoints were summarized by visit in the TFFU phase as described above using the M = E approach.

Pharmacokinetics/Pharmacodynamics:

No PK or PD analyses were performed for this report. All intensive PK and PBMC analyses summary statistics were included in the Interim Week 48 CSR.

Safety:

Adverse events were coded using the MedDRA Version 25.0. For the Week 384 safety analysis, cumulative OL safety data (treatment-emergent AEs, treatment-emergent laboratory abnormalities, etc) were summarized for participants in the OL Safety Analysis Set during the OL phase and for participants in the TFFU Safety Analysis Set during the TFFU phase. Exposure data were summarized for participants in the OL Safety Analysis Set during the OL phase only.

By-visit summary tables were presented for the entire study treatment period (DB and OL phase combined), based on participants in the Safety Analysis Set, starting from the DB phase baseline. Summaries for posttreatment-emergent AEs and laboratory abnormalities were generated for the TFFU phase. No by-visit summaries for safety measurements were generated

for the TFFU phase. All safety data including data collected during the TFFU phase were included in data listings.

A summary (number and percentage of participants) of bone events, fracture events, potential uveitis, and cardiovascular events was provided by treatment group for the OL phase based on participants in the OL Safety Analysis Set. Summaries of laboratory data using descriptive statistics were provided for the entire study period for participants in the Safety Analysis Set (from baseline to Week 384). Only laboratory abnormalities were summarized for participants in the TFFU Safety Analysis Set (from TFFU baseline to the end of study).

Other safety data (ie, clinical laboratory, hip and spine BMD, body weight, prior and concomitant medication, and ECG data) were summarized using descriptive statistics for continuous data and by the number and percentage of participants for categorical data. Vital signs data were presented in a listing.

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

A total of 873 participants were randomized and received at least 1 dose of study drug (TAF: 581 participants; overall TDF-TAF: 292 participants), of which 770 participants (TAF: 88.8%, 516 participants; overall TDF-TAF: 87.0%, 254 participants) completed DB study treatment. Overall, 339 participants entered OL treatment at Week 96 (TAF: 225 participants; overall TDF-TAF: 114 participants), and 428 participants remained on DB treatment from Week 96 to Week 144 and entered OL treatment at Week 144 (TAF: 289 participants; overall TDF-TAF: 139 participants).

Overall, 137 participants discontinued OL study treatment, of which 93 participants (16.0%) were in the TAF group and 44 participants (15.1%) were in the overall TDF-TAF group. The reasons for premature discontinuation of OL study treatment were withdrawal of consent (TAF: 8.1%, 47 participants; overall TDF-TAF: 7.5%, 22 participants), lost to follow-up (TAF: 2.1%, 12 participants; overall TDF-TAF: 3.1%, 9 participants), investigator's discretion (TAF: 1.7%, 10 participants; overall TDF-TAF: 0.7%, 2 participants), AE (TAF: 1.0%, 6 participants; overall TDF-TAF: 1.0%, 3 participants), pregnancy (TAF: 1.0%, 6 participants), protocol-specified criteria for withdrawal (TAF: 0.7%, 4 participants; overall TDF-TAF: 0.7%, 2 participants), HBsAg seroconversion (TAF: 0.5%, 3 participants; overall TDF-TAF: 1.4%, 4 participants), noncompliance with study drug (TAF: 0.5%, 3 participants; overall TDF-TAF: 0.7%, 2 participants), and lack of efficacy (TAF: 0.3%, 2 participants). As of the database finalization date, 636 participants (TAF: 72.8%, 423 participants; overall TDF-TAF: 72.9%, 213 participants) completed the protocol-planned duration of the study. A total of 163 participants entered the 24-week TFFU phase and 90 participants completed the TFFU phase.

Demographic and baseline characteristics for participants who entered the OL phase were generally similar between the treatment groups. The median age was 37 years (range: 18 to 69 years) in the TAF group and 37 years (range: 18 to 68 years) in the TDF-TAF groups (TDF-TAF Week 96, 37 years [range: 18 to 67 years]; TDF-TAF Week 144, 37 years [range: 19 to 68 years]). A smaller proportion of participants in the overall TDF-TAF group

compared with those in the TAF group were < 50 years of age at baseline (79.1% vs 84.2%, respectively).

Overall, the majority of participants were male (64.4%) and Asian (82.3%); 16.9% and 0.1% of participants, respectively, were White and of other race. The overall median (Q1, Q3) value for BMI at baseline was 23.7 (21.1, 26.2) kg/m^2.

Demographic and baseline characteristics were similar across treatment groups between participants dosed in the DB phase and participants entered in the OL phase of the study (GS-US-320-0110 Interim Week 48 CSR). Median baseline age was younger in participants entered in the TFFU phase compared to participants entered in the OL phase (33 years and 37 years, respectively). Other demographics and baseline characteristics were similar between the TFFU and OL phases.

Baseline disease characteristics were similar between treatment groups and to the overall participant population at study initiation. The median (Q1, Q3) baseline HBV DNA value overall was 7.9 (7.0, 8.6) log_{10} IU/mL. A similar proportion of participants in each treatment group had baseline ALT above the ULN based on the central laboratory normal range (TAF: 92.0%; TDF-TAF Week 96: 93.9%; TDF-TAF Week 144: 90.6%) and baseline ALT above the ULN based on the AASLD normal range (TAF: 97.5%; TDF-TAF Week 96: 97.4%; TDF-TAF Week 144: 96.4%). Overall, most participants were infected with HBV genotype C (54.0%) or genotype D (21.4%).

At baseline, the median (Q1, Q3) $eGFR_{CG}$ value was 108.6 (94.8, 129.0) mL/min in the TAF group, 110.1 (90.6, 131.9) mL/min in the TDF-TAF Week 96 group, and 105.6 (94.2, 123.6) mL/min in the TDF-TAF Week 144 group.

Although HBeAg positive at screening, 10 participants (1.9%) in the TAF group were HBeAg negative at their baseline visit. Similarly, 2 participants (1.8%) in the TDF-TAF Week 96 group and 2 participants (1.4%) in the TDF-TAF Week 144 group were HBeAg negative at their baseline visit. These 14 participants were included in the FAS.

At baseline, 9.5% of participants in the TAF group, 10.1% in the TDF-TAF Week 96 group, and 8.6% in the TDF-TAF Week 144 group reported a history of cirrhosis; 7.4% of participants in the TAF group, 4.5% in the TDF-TAF Week 96 group, and 8.8% in the TDF-TAF Week 144 group had a FibroTest score of ≥ 0.75, which was suggestive of cirrhosis (ie, equivalent to a Metavir score F4).

A similar percentage of participants in the overall TDF-TAF groups compared with participants in the TAF group had comorbidities of diabetes mellitus, cardiovascular disease, hypertension, or hyperlipidemia.

In the TFFU phase, original baseline disease characteristics were similar across treatment groups. The median (Q1, Q3) original baseline HBV DNA value overall was 8.0 (6.5, 8.6) log_{10} IU/mL. Original baseline ALT above the ULN based on the central laboratory normal range was as follows: TAF: 89.2%; TDF-TAF Week 96: 92.3%; TDF-TAF Week 144: 84.6% and original baseline ALT above the ULN based on the AASLD normal range was as follows: TAF: 96.4%; TDF-TAF Week 96: 100.0%; TDF-TAF Week 144: 92.3%. Five participants (4.5%) in the TAF group and 1 participant (1.9%) in the overall TDF-TAF group were HBeAg negative at their original baseline visit.

At baseline, 7.6% of participants in the TAF group and 2.6% in the overall TDF-TAF group reported a history of cirrhosis; 8.3% of participants in the TAF group and 2.1% in the overall TDF-TAF group had a FibroTest score of ≥ 0.75. Overall, most participants were infected with HBV genotype C (30.1%) or genotype D (35.0%).

A similar percentage of participants in the overall TDF-TAF groups compared with participants in the TAF group had comorbidities of diabetes mellitus, cardiovascular disease, hypertension, or hyperlipidemia.

Efficacy Results:

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

The results for the primary endpoint analysis were presented in the GS-US-320-0110 Interim Week 48 CSR. Similar rates of virologic suppression were achieved in the 2 treatment groups at Week 48 when assessed using the M = F method as follows: TAF 63.9%, 371 of 581 participants; TDF 66.8%, 195 of 292 participants; difference in proportions (baseline stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%. Because the lower bound of the 2-sided 95% CI of the difference (TAF – TDF) in the response rate was greater than the prespecified −10% margin, the TAF group met the primary endpoint of noninferiority to the TDF group. These results were subsequently confirmed in the GS-US-320-0110 Interim Week 96 CSR. HBV DNA suppression was maintained in both treatment groups through Week 96. The percentages of participants with HBV DNA levels < 29 IU/mL were as follows: TAF 72.8%, TDF 74.7%; difference in proportions (baseline stratum-adjusted): −2.2%, 95% CI: −8.3% to 3.9%.

The GS-US-320-0110 Interim Week 144 CSR presented results for the subset of participants who remained in the DB phase after Week 96. The rates of HBV DNA suppression were similar to those seen at Week 96 and were well maintained in the 2 treatment groups through Week 144. For the subset of participants who entered the OL phase at Week 96, rates of HBV DNA suppression were maintained from the OL baseline (Week 96) through Week 144 with similar rates of HBV DNA suppression seen in those continuing TAF treatment (DB TAF to OL TAF; TAF-TAF) and those who switched from DB TDF to OL TAF (TDF-TAF) at Week 96.

Overall, the rates of HBV DNA suppression (ie, HBV DNA < 29 IU/mL) were generally maintained after Week 144 through Week 384 in the TAF group and both TDF-TAF groups.

Using the M = F analyses, the proportion of participants with HBV DNA < 29 IU/mL at Week 384 was 66.2% (370 of 559 participants) in the TAF group, 63.8% (74 of 116 participants) in the TDF-TAF Week 96 group, and 67.9% (108 of 159 participants) in the TDF-TAF Week 144 group. These results were also similar to those reported during the DB treatment period.

Using the M = E analyses, the proportion of participants with HBV DNA < 29 IU/mL at Week 384 was 94.4% (370 of 392 participants) in the TAF group, 91.4% (74 of 81 participants) in the TDF-TAF Week 96 group, and 96.4% (108 of 112 participants) in the TDF-TAF Week 144 group. These results demonstrate that nearly all participants remaining on study treatment at Week 384 achieved the virologic endpoint of HBV DNA < 29 IU/mL.

Furthermore, across treatment groups, a high proportion (TAF group 59.7%, TDF-TAF Week 96 group 55.6%, and TDF-TAF Week 144 group 55.4%) achieved complete suppression (HBV DNA < 29 IU/mL with target not detected) at Week 384.

As expected for participants discontinuing OAVs during the TFFU phase, using the M = E analyses, the proportions of participants with HBV DNA < 29 IU/mL decreased progressively from the TFFU baseline through to TFFU Week 24. The proportion of participants with HBV DNA < 29 IU/mL at TFFU baseline was as follows: TAF 89.0% (97 of 109 participants) and overall TDF-TAF 82.7% (43 of 52 participants). At TFFU Week 24, the proportion of participants with HBV DNA < 29 IU/mL was as follows: TAF 38.6% (22 of 57 participants) and overall TDF-TAF 17.9% (5 of 28 participants).

Mean (SD) changes from baseline in HBV DNA levels at Week 384 were similar across treatment groups and were as follows: TAF −6.20 (1.560) $\log_{10}$ IU/mL; TDF-TAF Week 96 −5.98 (1.754) $\log_{10}$ IU/mL, and TDF-TAF Week 144 −6.31 (1.461) $\log_{10}$ IU/mL.

During the TFFU phase, mean (SD) TFFU baseline HBV DNA levels for participants in the TFFU FAS were as follows: TAF 1.68 (1.438) $\log_{10}$ IU/mL and overall TDF-TAF 1.74 (1.255) $\log_{10}$ IU/mL. HBV DNA levels increased similarly across treatment groups from TFFU baseline to TFFU Week 8, after which levels remained stable across the treatment groups through the end of the TFFU phase.

Using the M = F or M = E analyses, the proportion of participants that achieved ALT normalization was higher in the TAF group compared with the TDF-TAF groups during the DB treatment period based on the central laboratory criteria and AASLD criteria. Generally, ALT normalization rates increased in both TDF-TAF groups when participants were switched to TAF.

Using the M = F analyses, at Week 384, ALT normalization rates based on the central laboratory criteria were 60.0% (310 of 517 participants) in the TAF group, 56.5% (61 of 108 participants) in the TDF-TAF Week 96 group, and 59.0% (85 of 144 participants) in the TDF-TAF Week 144 group. Missing data in the OL phase likely contributed to the decline in ALT normalization rates over time in this longitudinal study. The ALT normalization rates based on the AASLD criteria were 54.1% (295 of 545 participants) in the TAF group, 48.2% (55 of 114 participants) in the TDF-TAF Week 96 group, and 54.2% (83 of 153 participants) in the TDF-TAF Week 144 group.

Using the M = E analyses, at Week 384, ALT normalization rates based on the central laboratory criteria were 86.1% (310 of 360 participants) in the TAF group, 80.3% (61 of 76 participants) in the TDF-TAF Week 96 group, and 87.6% (85 of 97 participants) in the TDF-TAF Week 144 group. The ALT normalization rates at Week 384 according to the AASLD criteria were 77.6% (295 of 380 participants) in the TAF group, 69.6% (55 of 79 participants) in the TDF-TAF Week 96 group, and 80.6% (83 of 103 participants) in the TDF-TAF Week 144 group.

For the TFFU phase, when using the M = E approach, the proportion of participants with normal ALT at TFFU baseline by central laboratory criteria was 80.7% (88 of 109 participants) in the TAF group and 71.2% (37 of 52 participants) in the overall TDF-TAF group. The proportion of participants with normal ALT at TFFU Week 24 was 62.5% (35 of

56 participants) in the TAF group and 53.6% (15 of 28 participants) in the overall TDF-TAF group.

For the TFFU phase, when using the M = E approach, the proportion of participants with normal ALT at TFFU baseline by AASLD criteria was 69.7% (76 of 109 participants) in the TAF group and 59.6% (31 of 52 participants) in the overall TDF-TAF group. The proportion of participants with normal ALT at TFFU Week 24 was 50.0% (28 of 56 participants) in the TAF group and 35.7% (10 of 28 participants) in the overall TDF-TAF group.

The proportion of participants that achieved HBeAg loss using the M = F analyses progressively increased with duration of treatment and was 31.4% (171 of 544 participants) in the TAF group, 28.6% (32 of 112 participants) in the TDF-TAF Week 96 group, and 32.1% (50 of 156 participants) in the TDF-TAF Week 144 group at Week 384. Similarly, the proportion of participants that achieved HBeAg seroconversion increased over time with 21.0% (114 of 544 participants) in the TAF group, 17.9% (20 of 112 participants) in the TDF-TAF Week 96 group, and 23.1% (36 of 156 participants) in the TDF-TAF Week 144 group achieving this endpoint at Week 384. Similar serological results were seen across treatment groups for HBeAg loss at Week 384 and HBeAg seroconversion when evaluated by the M = E analyses method.

During the study, the proportions of participants that achieved HBsAg loss and HBsAg seroconversion were low by both M = F and M = E approaches. The proportion of participants that achieved HBsAg loss at Week 384 using the M = F analyses was 1.6% (9 of 554 participants) in the TAF group, 3.6% (4 of 112 participants) in the TDF-TAF Week 96 group, and 1.9% (3 of 159 participants) in the TDF-TAF Week 144 group. The proportion of participants that achieved HBsAg seroconversion at Week 384 was 1.1% (6 of 554 participants) in the TAF group, 3.6% (4 of 112 participants) in the TDF-TAF Week 96 group, and 1.9% (3 of 159 participants) in the TDF-TAF Week 144 group. Similar serological results were seen across treatment groups for HBsAg loss at Week 384 and HBsAg seroconversion when evaluated by the M = E analyses method.

In this study, FibroTest was included as a noninvasive means for assessing changes in liver fibrosis during the study period. Overall, the TAF and TDF-TAF groups demonstrated similar shift patterns in fibrosis score categories by FibroTest at Week 384. The majority of participants with baseline 0.00 to 0.48 FibroTest scores maintained their status at Week 384 in the TAF group (94.8%, 272 of 287 participants) and the overall TDF-TAF group (92.6%, 126 of 136 participants). Most participants with baseline 0.49 to 0.74 FibroTest scores (Metavir F2 to F3; moderate to severe fibrosis) maintained or improved their status at Week 384 in the TAF group (maintained: 40.7%, 24 of 59 participants; improved: 55.9%, 33 of 59 participants) and the overall TDF-TAF group (maintained: 48.4%, 15 of 31 participants; improved: 38.7%, 12 of 31 participants).

For participants in both the TAF and TDF-TAF groups with available baseline 0.75 to 1.00 FibroTest scores (Metavir F4; cirrhosis), a clinically significant proportion of participants had improved FibroTest score categories at Week 384. For participants in the TAF group, 46.9% (15 of 32 participants) and 21.9% (7 of 32 participants) improved to 0.49 to 0.74 and 0.00 to 0.48 FibroTest score categories, respectively, at Week 384. For participants in the overall TDF-TAF group, 46.7% (7 of 15 participants) and 20.0% (3 of 15 participants) improved to 0.49 to 0.74 and 0.00 to 0.48 FibroTest scores, respectively, at Week 384. The proportions of

participants in both groups with a FibroTest score of 0.75 to 1.00 were smaller (ie, the majority of participants did not have cirrhosis based on FibroTest score); however, even given this limitation, the majority of participants with available data improved their FibroTest stage at Week 384.

The clinical relevance of the small mean changes in FibroTest scores is unknown.

In summary, over 384 weeks of treatment, participants randomized to receive TAF in the DB and OL phases, and those randomized to TDF who rolled over to OL TAF at either Week 96 or Week 144 showed high rates of virologic suppression and ALT normalization, improved FibroTest score categories (particularly in the 0.75 to 1.00 range), and progressive increases in rates of HBeAg loss/seroconversion, while rates of HBsAg loss/seroconversion were low.

Pharmacokinetics/Pharmacodynamics Results: No PK or PD analyses were performed for this report.

Safety Results:

Adverse Events

For this report, cumulative safety data (treatment-emergent AEs, treatment-emergent laboratory abnormalities, etc.) were summarized for participants in the OL Safety Analysis Set during the OL phase and participants in the TFFU Safety Analysis Set during the TFFU phase. By-visit summary tables for key renal, bone, and lipid data were presented for the entire study treatment period (DB and OL phase combined), based on participants in the Safety Analysis Set, starting from the DB phase at baseline.

Summaries for posttreatment-emergent AEs and laboratory abnormalities were generated for the TFFU phase. Only laboratory abnormalities were summarized for participants in the TFFU Safety Analysis Set (from TFFU baseline to the end of study).

During the OL phase, 514 participants in the TAF group, 114 participants in the TDF-TAF Week 96 group, and 139 participants in the TDF-TAF Week 144 group were included in the OL Safety Analysis Set.

During the OL phase, treatment with TAF was safe and well tolerated across the 3 treatment groups. The observed overall incidence of any AE during the OL phase was similar between treatment groups (TAF: 67.1%, 345 participants; TDF-TAF Week 96: 71.1%, 81 participants; TDF-TAF Week 144: 66.9%, 93 participants).

Most AEs were Grade 1 (mild) or Grade 2 (moderate) and were considered unrelated to study drug by the investigator. A similar percentage of participants in each treatment group experienced Grade 3 or 4 AEs (TAF: 8.0%, 41 participants; overall TDF-TAF: 5.9%, 15 participants). Two participants (0.4%) in the TAF group experienced a Grade 3 or 4 study drug-related AE in the OL phase (renal neoplasm and cerebrovascular accident, both serious adverse events [SAEs]).

The incidences of SAEs during the OL phase were similar between treatment groups: 11.5% (59 participants) in the TAF group and 12.6% (32 participants) in the overall TDF-TAF group. Four participants (0.8%), all in the TAF group, had SAEs that were considered related to the

study drug; 1 participant (0.2%) each of ALT increased, osteonecrosis, renal neoplasm, and cerebrovascular accident.

Three participants (0.6%) in the TAF group had a study drug interruption due to an AE. Six participants (1.2%) in the TAF group and 3 participants (1.2%) in the overall TDF-TAF group experienced an AE leading to discontinuation of study drug during OL phase. There were no deaths during the OL phase of the study.

During the TFFU phase, the incidence of any AE was 27.0% (30 participants) in the TAF group, and 19.2% (10 participants) in the overall TDF-TAF group. Adverse events related to HBV exacerbation were reported in 16 participants total (12 and 4 participants in the TAF and overall TDF-TAF groups, respectively). Serious AEs were reported for 3.6% (4 participants) in the TAF group and 1.9% (1 participant) in the overall TDF-TAF group.

The majority of the AEs reported during the TFFU phase were Grade 1 or 2 in severity. Grade 3 AEs reported by ≥ 2 participants in any group were AEs related to HBV exacerbation: hepatitis (TAF: 1.8%, 2 participants), hepatitis B (TAF: 1.8%, 2 participants; overall TDF-TAF: 3.8%, 2 participants), and ALT increased (TAF: 1.8%, 2 participants; overall TDF-TAF: 1.9%, 1 participant). There were no Grade 4 AEs reported during the TFFU phase.

During the TFFU phase, ALT elevations occurred in 23 of 163 participants overall (14.1%): 12 participants (10.8%) in the TAF group and 11 participants (21.2%) in the overall TDF-TAF group. Six of 163 participants overall (3.7%) experienced posttreatment ALT flare: 3 participants (2.7%) in the TAF group and 1 participant (3.8%) in the overall TDF-TAF group.

Bone Safety

The incidence of bone events (based on relevant MedDRA bone preferred terms) during the OL phase was similar across treatment groups (TAF: 9.5%, 49 participants; overall TDF-TAF: 7.9%, 20 participants). Two participants in the TAF group discontinued study drugs due to bone events: one each for osteonecrosis and osteoporosis.

A total of 7 participants (1.4%) in the TAF group and 6 participants (2.4%) in the overall TDF-TAF group experienced a fracture event during the OL phase. All fractures were considered unrelated to the study drug by the investigators, none resulted in discontinuation of study drug, and 11 out 13 fractures were trauma-related. The majority of participants with AEs related to BMD abnormalities had associated risk factors, including osteopenia (hip and/or spine) at baseline or during DB phase while on TDF treatment, and/or vitamin D deficiency at baseline, and/or were female ≥ 50 years of age at the time of the AE onset.

The mean BMD baseline values for both hip and spine BMD were similar between the treatment groups. For participants in the TAF group, the percentage change from original baseline in BMD demonstrated minimal declines for the hip and spine, which were relatively stable through Week 384. In contrast, for participants in the TDF-TAF Week 96 and TDF-TAF Week 144 groups, mean percentage declines from original baseline in hip and spine were observed for the first 96 and 144 weeks, respectively of DB treatment with TDF. After switching to OL TAF treatment, mean percentage changes in BMD improved compared with DB TDF treatment, indicative of recovery of BMD loss at both sites. Across treatment groups,

the majority of participants with normal hip or spine BMD or osteopenia at baseline retained their BMD clinical status at Week 384.

Renal Safety

Overall, renal AEs were uncommon during OL phase, and the majority were not related to the study drug and resolved with the study drug continued.

Renal AEs occurring in ≥ 2 participants for each treatment group were as follows: TAF: nephrolithiasis (2.1%, 11 participants), renal cyst (1.0%, 5 participants), hematuria (0.8%, 4 participants), pollakiuria, proteinuria, and ureterolithiasis (each 0.6%, 3 participants), and hydronephrosis (0.4%. 2 participants); TDF-TAF Week 96: hematuria (1.8%, 2 participants); and TDF-TAF Week 144: nephrocalcinosis (1.4%, 2 participants).

When assessed according to change from original baseline, there were minimal changes in serum creatinine observed at Week 384 between the treatment groups. Overall, creatinine was stable through the study in all groups with small mean (SD) changes of 0.007 (0.1102) mg/dL from baseline at Week 384 in the TAF group, and slight improvement after switching from TDF in the TDF-TAF Week 96 group (−0.006 [0.1024] mg/dL at Week 384 vs 0.026 [0.0877] mg/dL increase at Week 96) and in the TDF-TAF Week 144 group (0.013 [0.1084] mg/dL at Week 384 vs 0.029 [0.0940] at Week 144).

When assessed according to change from original baseline, there were minimal median decreases in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ observed at Week 384 between the treatment groups, while median eGFR values (both, $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$) remained above 100 (mL/min and mL/min/1.73 m^2, respectively) during TAF treatment.

No participant in any treatment group experienced an AE of proximal tubulopathy (including Fanconi syndrome), and no participant experienced renal impairment or failure.

Cardiovascular Events

The incidence of potential cardiovascular events (which included creatine phosphokinase increase, cerebrovascular and cardiovascular events) during the OL phase was low and similar across treatment groups (TAF: 2.3%, 12 participants; overall TDF-TAF: 1,6%, 4 participants). All participants that experienced cerebrovascular and cardiovascular events had relevant risk factors, including elderly age, and/or medical history of hypertension, diabetes, or preexisting cerebrovascular or cardiovascular condition, and/or elevated lipids at baseline. None of these events resulted with study drug discontinuation.

Hepatocellular Carcinoma (HCC) Events

Five participants (TAF: 0.4%, 2 participants; TDF-TAF Week 96: 2.6%, 3 participants; TDF-TAF Week 144: 0%) experienced an AE of HCC in the OL phase.

Laboratory Abnormalities

The majority of laboratory abnormalities were Grade 1 or 2. A similar proportion of participants across treatment groups had Grade 3 or 4 laboratory abnormalities in the OL phase (TAF: 25.6%, 131 participants and overall TDF-TAF: 25.1%, 63 participants).

The majority of laboratory abnormalities in the TFFU phase were Grade 1 or 2. A similar proportion of participants had Grade 3 or 4 laboratory abnormalities across treatment groups in the TFFU phase (TAF: 33.0%, 36 participants; overall TDF-TAF: 31.4%, 16 participants).

Lipid Parameters

Overall, lipid parameters were relatively stable through Week 384 in participants in the TAF group with small median increases from original baseline. For participants in the TDF-TAF groups, decreases in all fasting lipid parameters were observed during the DB phase. Following the switch to OL TAF, increases in fasting lipid parameters were observed. This increase is known as the removal of the "lipid lowering effect" with TDF. The median (Q1, Q3) changes from baseline to Week 384 in total cholesterol to high-density lipoprotein (HDL) ratio were low and similar in both, TAF and TDF-TAF groups (TAF 0.5 [0.0, 1.1]; TDF-TAF 0.5 [0.1, 1.0]), supporting lack of clinical relevance of median changes in individual lipid parameters during TAF treatment. During the OL phase, the majority of participants with Grade 3 fasting low-density lipoprotein (LDL) cholesterol had graded LDL cholesterol abnormalities at original baseline (TAF group) or OL baseline (overall TDF-TAF group). Grade 3 LDL cholesterol elevations were mainly transient and improved to Grade 1 or 2 or normal values by the last study visit during OL phase. Lipid modifying agents were initiated for a small number of participants with a transient Grade 3 LDL cholesterol abnormalities.

CONCLUSIONS:

The conclusions from this final analysis of Study GS-US-320-0110 are as follows:

- Overall, the rates of HBV DNA suppression were generally high and well maintained after Week 144 through Week 384 in the TAF group and both TDF-TAF groups.
- The proportion of participants that achieved ALT normalization was higher in the TAF group compared with the TDF-TAF groups during the DB treatment period. Generally, ALT normalization rates increased in both TDF-TAF groups when participants were switched to TAF. ALT normalization rates were similar across treatment groups at Week 384.
- The proportion of participants that achieved HBeAg loss and seroconversion progressively increased with duration of treatment across treatment groups. The proportions of participants that achieved HBsAg loss and HBsAg seroconversion were low.
- Switching from TDF to TAF resulted in continuing high efficacy through Week 384 as demonstrated by similar rates of HBV DNA suppression and increased rates of ALT normalization.
- Overall, there were no new safety issues in the OL analyses of participants in the TAF and TDF-TAF groups who switched to OL TAF. In participants who switched from TDF to TAF, the types and frequencies of AEs between the treatment groups were generally similar in the OL phase.

- TAF and TDF were generally well tolerated as demonstrated by the low proportions of participants who had Grade 3 or 4 AEs, SAEs, or who discontinued study drugs due to AEs in the OL phase. The types and frequencies of AEs were similar between the TAF and TDF groups and comparable to results observed at the Week 144 data cutoff.
- Overall, fasting lipid parameters were relatively stable through Week 384 in participants in the TAF group with small median increases from original baseline. Following the switch to OL TAF, increases in fasting lipid parameters were observed in the TDF-TAF group. This increase is consistent with the removal of the known lipid lowering effect of TDF. The median changes from baseline to Week 384 in total cholesterol to HDL ratio were low and similar in both, TAF and TDF-TAF groups, supporting lack of clinical relevance of median changes in individual lipid parameters during TAF treatment.
- At Week 384, participants receiving TAF in the OL phase demonstrated improved bone and renal safety parameters compared with TDF, which were consistent with prior results at Weeks 48, 96, and 144.