CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208464
Supplement #:	S-000
Drug Name:	Tenofovir Alafenamide (Vemlidy®, TAF) 25-mg QD
Indication(s):	Treatment of Chronic HBeAg-Negative and HBeAg-Positive Hepatitis B
Applicant:	Gilead
Date(s):	Received Date: January 11, 2016 Midcycle Meeting: June 7, 2016 Primary Review Date: October 7, 2016 PDUFA Date: November 11, 2016
Review Priority:	Standard
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Keywords: tenofovir alafenamide, Vemlidy®, TAF, hepatitis B virus (HBV), HBeAg-Negative, HBeAg-Positive

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1 EXECUTIVE SUMMARY

The review will focus on the applicant's two ongoing prospective, randomized, active-controlled, double-blind, phase 3 studies in hepatitis B e antigen (HBeAg)-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects with chronic hepatitis B (CHB), including a subset with compensated cirrhosis at study entry. In both of these similarly designed noninferiority (NI) studies, subjects are randomized to receive either TAF or tenofovir disoproxil fumarate (TDF, Viread®) for 96 weeks. The clinical study reports submitted in this NDA describe the results of each study through a data cutoff performed when all randomized subjects had completed the Week 48 visit or had discontinued from study drugs before their Week 48 visit.

In the primary efficacy analysis in Study GS-US-320-0108 the percentage of subjects with HBV DNA<29 IU/mL at Week 48 was 94% in the TAF 25 mg arm and 93% in the TDF 300 mg arm. The corresponding risk difference was +1.7% in favor of TAF with 95% CI of -4% to +7%. Therefore, it appeared that NI was demonstrated as the lower bound of the 95% CI was much larger than the NI margin of -10%.

In the primary efficacy analysis in Study GS-US-320-0110 the percentage of subjects with HBV DNA<29 IU/mL at Week 48 was 64% in the TAF 25 mg arm and 67% in the TDF 300 mg arm. The corresponding risk difference was -3.5% in favor of TDF the 95% CI ranging from -9.7% to +2.6%. The applicant concluded that TAF was NI to TDF since the lower bound of the 2-sided 95% CI of the difference (TAF group – TDF group) in the proportion of subjects who achieved HBV DNA < 29 IU/mL at Week 48 was greater than −10%.

However in both trials, particularly in Study GS-US-320-0110, homogeneity of the TAF treatment effect appeared to be questionable for baseline viral load, a key baseline covariate used as a stratification variable at randomization. Patients with higher baseline viral loads ($\geq$7 $\log_{10}$ IU/mL) had higher response rates in the TDF arm compared to the TAF arm and the reverse trend was observed for subjects with lower baseline viral loads. The treatment by baseline HBV DNA viral load interaction was statistically significant in Study GS-US-320-0110 and the same trend was observed in Study GS-US-320-0108. Due to a lack of homogeneity of the treatment effect in subjects with low and high viral loads, the conclusion of NI of TAF to TDF may only be valid for subjects with lower viral loads of <7 $\log_{10}$ IU/mL.

The applicant also concluded that higher rates of alanine aminotransferase (ALT) normalization were seen with TAF than with TDF and that the differences were statistically significant when evaluated by the AASLD criteria. The applicant pre-specified the order of hypothesis testing in the statistical analysis plan (SAP) and since their ordered list of multiple endpoints did not include ALT normalization there was no control of the type I error rate. However, there is less concern about pre-specification of type I error since the statistically significant finding was observed in both trials. The same trend was observed using central laboratory normal ranges but there was no statistically significant difference between TAF and TDF in either trial.

When the cutoff of 7 $\log_{10}$ IU/mL was used for study GS-US-320-0110 the Zelen test for the treatment by baseline HBV DNA interaction for ALT normalization (using the AASLD criteria) was statistically significant (p=0.006) at the 0.05 level. For subjects with baseline HBV DNA<7 $\log_{10}$ IU/mL the difference between TAF and TDF was 26% (favoring TAF) while there was no statistically significant difference between the two treatment groups for subjects with baseline viral loads ≥7 $\log_{10}$ IU/mL. The treatment by baseline HBV DNA interaction for ALT normalization was not statistically significant in the HBeAg-Negative trial.

2 INTRODUCTION

2.1 Overview

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits reverse transcription in HIV-1 and HBV. Tenofovir disoproxil fumarate (TDV; Viread®), an oral prodrug of TFV is approved for the treatment of HIV infection to be given in combination with other antiretroviral (ARV) agents and is approved for treatment of chronic hepatitis B as monotherapy. TDF is associated with nephrotoxicity and bone-related toxicity in some patients.

Tenofovir alafenamide (TAF) is an investigational prodrug of TFV. The applicant claims that distinct metabolism of TAF offers the potential for an improved clinical profile when compared with TDF. The applicant cited recent results from a large dataset of 1733 HIV-infected, treatment-naive subjects randomized to receive treatment with the fixed-dose combination (FDC) of elvitegravir, cobicistat, emtricitabine, and TAF (E/C/F/TAF) or elvitegravir, cobicistat, emtricitabine, and TDF (STB; Stribild®; E/C/F/TDF) as an FDC. According to the applicant, renal and bone effects were significantly reduced in subjects who received E/C/F/TAF at Week 48.

Table 1: List of all studies included in the review

	Phase and Design	Treatment Duration / Interim Reporting Period	# of Subjects per Arm (efficacy analysis Tested/ control)	Study Population
GS-US-320-0108	Phase 3, Randomized, Double-Blind Trial	96 weeks / Week 48	285 TAF 25 mg / 140 TDF 300 mg	HBeAg-negative subjects with chronic hepatitis B infection
GS-US-320-0110	Phase 3, Randomized, Double-Blind Trial	96 weeks / Week 48	581 TAF 25 mg / 292 TDF 300 mg	HBeAg-positive subjects with chronic hepatitis B infection

The review will focus on the applicant's two ongoing prospective, randomized, active-controlled, double-blind phase 3 studies in hepatitis B e antigen (HBeAg)-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects with CHB, including a subset with compensated cirrhosis at study entry. In both of these similarly designed noninferiority studies, subjects are randomized to receive either TAF or TDF for 96 weeks. The clinical study reports submitted in this NDA describe the results of the study through a data cutoff performed when all randomized subjects had completed the Week 48 visit or had discontinued from study drugs before their Week 48 visit.

2.2 Data Sources

The application package is located at: \\CDSESUB1\evsprod\NDA208464\0000. Both SDTM and ADAM datasets were submitted along with the applicant's SAS programs. The statistical reviewer's analyses were primarily based on the analysis datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted data that were well defined as were summary tables and figures in the clinical study report. There appeared to be good agreement between results obtained using analysis and raw datasets.

3.2 Evaluation of Efficacy

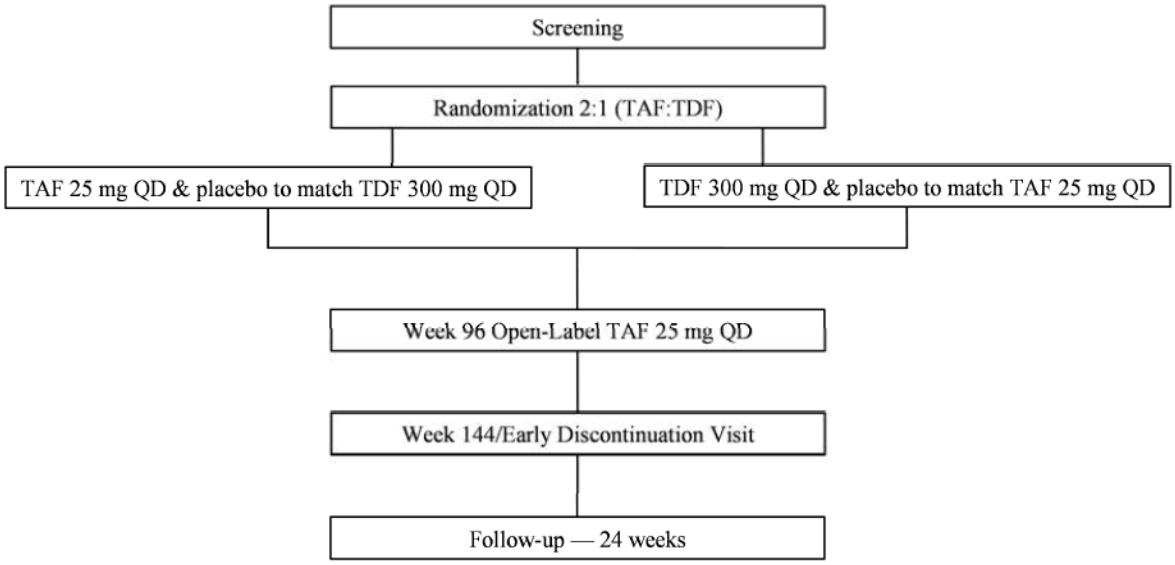
3.2.1 Study Design and Endpoints

Studies GS-US-320-0108 and GS-US-320-0110 are ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter trials comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of CHB infection in treatment-naive and treatment-experienced subjects. Subjects in Study GS-US-320-0108 were HBeAg-Negative while subjects in Study GS-US-320-0110 were HBeAg-Positive.
Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups:

- **TAF group:** TAF 25 mg once daily and matched placebo of TDF 300 mg once daily for 96 weeks
- **TDF group:** TDF 300 mg once daily and matched placebo of TAF 25 mg once daily for 96 weeks

Subjects who complete 96 weeks of double-blind treatment may begin an open-label extension period to receive 25 mg TAF once daily for up to an additional 48 weeks (ie, Weeks 96 through 144).

Figure 1: Study Schema of Phase 3 Trials



QD = once daily; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Source: Figure 7-1 of the Clinical Study Report for GS-US-320-0108

Stratified Randomization

In Study GS-US-320-0108 randomization was stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 to < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL) and OAV treatment status (treatment naive versus treatment experienced) at screening. In Study GS-US-320-0110 randomization was stratified by plasma HBV DNA level (< 8 $\log_{10}$ IU/mL versus ≥ 8 $\log_{10}$ IU/mL) and OAV treatment status (treatment naive versus treatment experienced) at screening.

The Roche COBAS® TaqMan® HBV test for use with the High Pure System was used to measure plasma HBV DNA in this study and is the same assay utilized in the Phase 3 studies leading to TDF registration for treatment of CHB infection (Studies GS-US-174-0102 and GS-US-174-0103). This assay was deemed the most appropriate because TDF is the comparator in this prospective, randomized, double-blind noninferiority study. The lower limit of quantification in plasma for the assay is 29 IU/mL, which is the primary endpoint cutoff for viral suppression. Levels of hepatitis B surface antigen (HBsAg) were quantified in serum by the Abbott Architect assay, with a lower limit of quantification of ≤ 0.05 IU/mL.

The primary efficacy endpoint was the proportion of subjects with HBV DNA < 29 IU/mL at Week 48. Secondary efficacy endpoints evaluated for the Week 48 analysis included the proportion of subjects with HBeAg loss and seroconversion to the antibody against the hepatitis B e antigen (anti-HBe), plasma HBV DNA < 29 IU/mL (target not detected), ALT normalization, HBsAg loss and seroconversion to the antibody against the hepatitis B surface antigen (anti-HBs), change from baseline in fibrosis, and incidence of drug-resistant mutations.

3.2.2 Statistical Methodologies

According to the applicant, the primary efficacy analysis was conducted after the last randomized subject reached Week 48 or discontinued study drugs prematurely. A missing = failure (M = F) approach was employed. The primary efficacy analysis used the Full Analysis Set (FAS), which included all subjects who were randomized into the study and received at least 1 dose of study drugs.

The Per-Protocol (PP) Analysis Set included all subjects who were randomized into the study, received at least 1 dose of study drugs, and had not been excluded based on the criteria below. Subjects were analyzed according to the treatment they actually received. The PP Analysis Set was the secondary analysis set for efficacy analyses.

Subjects meeting any of the following criteria were excluded from the Week 48 PP Analysis Set:

- Subjects who did not have on-treatment HBV DNA in the Week 48 analysis window, except for subjects who discontinued study drugs due to lack of efficacy (Note: lack of efficacy was defined as having the check-box for "Lack of Efficacy" marked as the reason for premature study drug discontinuation on the study drug completion eCRF page.)
- Subjects who met the exclusion criterion for receiving ongoing therapy with any of the prohibited medications listed in Section 4.3 of the protocol (Appendix 16.1.1)
- Subjects with an adherence rate for active study drug up to the Week 48 visit below the 2.5th percentile

Sample Size Estimates

For Study GS-US-320-0108 sample sizes of 130 and 260 subjects in the TDF and TAF groups, respectively, were planned to give 90% power to rule out the NI margin of 10% at a 1-sided significance level of 0.025. According to the applicant, this sample size was based on the assumption that the expected difference (TAF−TDF) in proportion of subjects with HBV DNA < 29 IU/mL was 0 and the proportion of subjects with HBV DNA < 29 IU/mL in the TDF group was 91%. A similar response rate in the TDF group was observed in the pivotal Phase 3 study supporting the Viread marketing application that evaluated TDF in HBeAg-negative subjects with CHB infection (Study GS-US-174-0102).

For Study GS-US-320-0110 sample sizes of 288 and 576 subjects in the TDF and TAF groups, respectively, were planned to give 84% power to rule out the NI margin of 10% at a 1-sided significance level of 0.025. This sample size based on the assumption that the expected

difference (TAF−TDF) in the proportion of subjects with HBV DNA < 29 IU/mL was 0 and the proportion of subjects with HBV DNA < 29 IU/mL in the TDF group was 69%. A similar response rate in the TDF group was observed in the pivotal Phase 3 study supporting the Viread marketing application that evaluated TDF in HBeAg-positive subjects with CHB infection (Study GS-US-174-0103).

Primary Efficacy Analyses

The purpose of the primary efficacy endpoint analysis was to assess the NI of the treatment with TAF relative to the treatment with TDF. The NI margin was pre-specified by Gilead to be 10%. According to Dr. Thomas Hammerstrom's review of the protocol (IND 115-561 SDN 012) the 10% NI margin would be acceptable, given the TDF was approved on the basis of trials showing TDF to be superior to adefovir by considerably more than 10% in both HBeAg-Negative and HBeAg-Positive subjects.

For Study GS-US-320-0108 the baseline HBV DNA level (< 7 log10 IU/mL, ≥7 to < 8 log10 IU/mL, ≥ 8 log10 IU/mL) and OAV treatment status (treatment-naive versus treatment-experienced) were used in the stratum-stratified, 2-sided Mantel-Haenszel test. For Study GS-US-320-0110 the baseline HBV DNA level (< 8 log10 IU/mL versus ≥ 8 log10 IU/mL) and OAV treatment status (treatment-naive versus treatment-experienced) were used in the stratum-stratified, 2-sided Mantel-Haenszel test. The applicant concluded that TAF was not inferior to TDF if the lower bound of the 2-sided 95% CI of the difference (TAF group – TDF group) in the proportion of subjects who achieved HBV DNA < 29 IU/mL at Week 48 was greater than −10%.

The reviewer computed both unadjusted and adjusted risk differences of (TAF-TDF) response rates and corresponding 95% CIs and p-values for the primary efficacy variable. The unadjusted analysis was performed for comparative purposes to see how much of a confounding effect the stratification variables had on the primary efficacy analysis. Unlike the adjusted analysis, the unadjusted analysis provided exact 95% CIs for the risk difference.

Exact 95% CIs were computed for unadjusted risk differences using the proc StatXact procedure proc binomial with two-sided tests using the standardized (score) statistic. The reviewer computed adjusted 95% CIs using the Mantel-Haenszel approach stratified using the same baseline HBV DNA categories for both trials (<7, 7 to <8, and ≥8 $\log_{10}$ IU/mL) and oral antiviral treatment status for treatment experienced (TE) and treatment naïve (TN) status. Unlike the reviewer the applicant used different baseline HBV DNA categories for the two trials (<7, 7 to <8, and ≥8 $\log_{10}$ IU/mL for Study GS-US-320-0108 and <8 and ≥8 $\log_{10}$ IU/mL for Study GS-US-320-0110).

Forest plots of risk differences of (TAF minus TDF) response rates and corresponding tables for subgroup analyses were created by the statistical analyst with statistical input from the reviewer. Unadjusted 95% CIs of risk differences were computed using the proc StatXact procedure proc binomial with two-sided tests using the standardized (score) statistic. Zelen's exact test was used to assess homogeneity of treatment effects.

If there were more than 10% of subjects with major protocol deviations, the applicant stated that a per protocol analysis was to be performed on the primary endpoint, based on all ITT subjects,

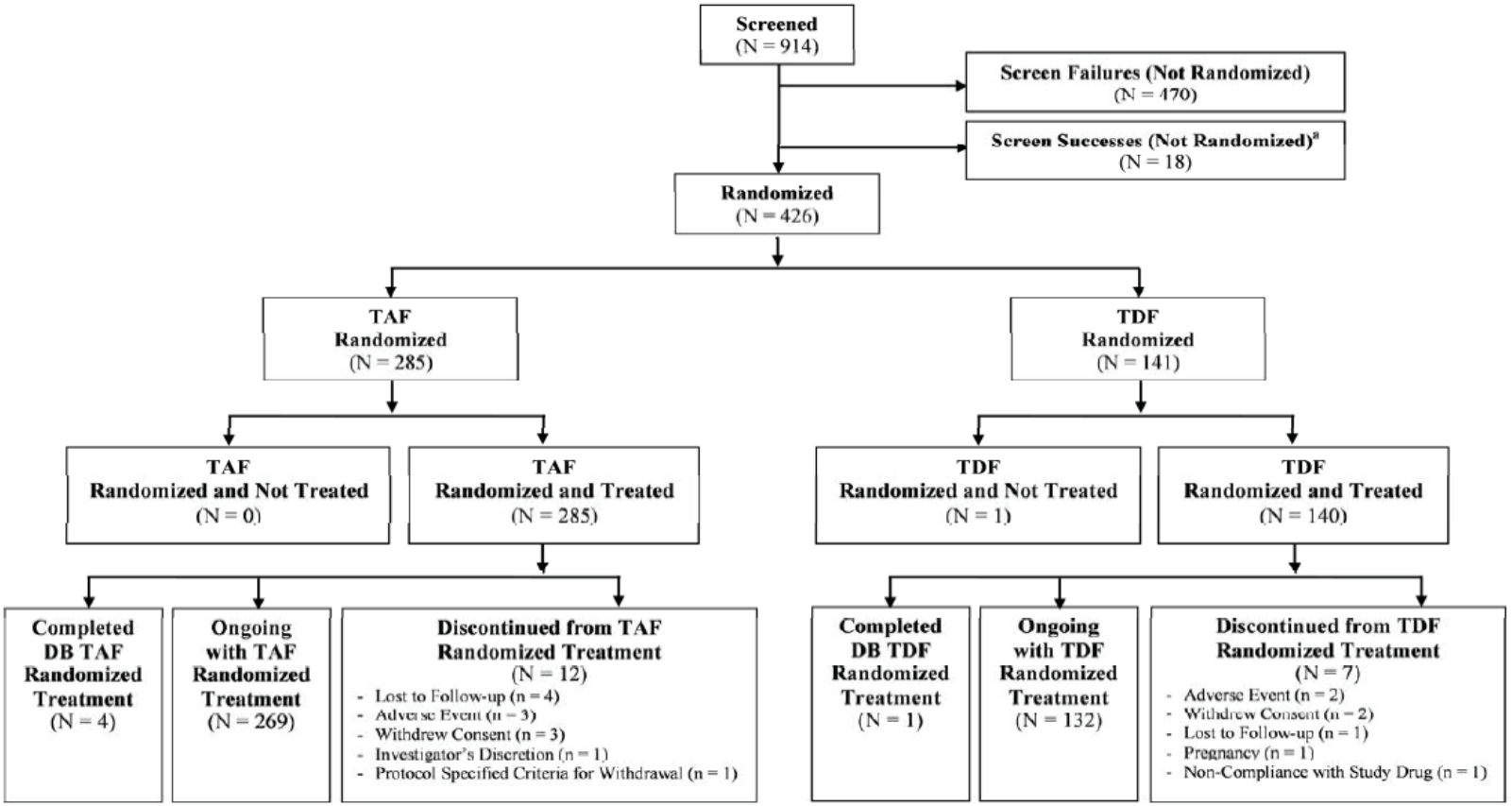
excluding the subjects with major protocol deviations. Since the overall percentage of subjects with a major protocol deviation was <10% in both trials, no per protocol analyses were performed.

Note that the applicant also proposed multiplicity adjustments for secondary efficacy endpoints. See the Appendix for details.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Figure 2: Disposition of Study Subjects (GS-US-320-0108)



DB = double blind

a For screen successes but not randomized, 14 were due to withdrawal of consent and 4 were due to outside of visit window.

Data cutoff date was 01 October 2015.

Source: Figure 8-1 of the Clinical Study Report

Table 2: Subjects Screened, Enrolled, Treated: All Subjects (Study GS-US-320-0108)

	TAF 25 mg	TDF 300 mg	Total
Subjects Screened			914
Subjects Not Randomized			
Screen Failure Subjects Who Were Not Randomized			470
Subjects Met All Eligibility Criteria and Not Randomized[a]			18
Subjects in Randomized Analysis Set	285	141	426
Subjects Randomized and Never Treated[b]	0	1	1
Subjects in Safety Analysis Set	285	140	425
Subjects in Full Analysis Set (FAS)	285	140	425
Subjects Remaining on Double-Blind Study Treatment up to the Data Cutoff Date	269 (94.4%)	132 (94.3%)	401 (94.4%)
Subjects Prematurely Discontinued Double-Blind Study Treatment Prior to the Data Cutoff Date	12 (4.2%)	7 (5.0%)	19 (4.5%)
Reasons for Prematurely Discontinued from Double-Blind Study Treatment			
Adverse Event	3 (1.1%)	2 (1.4%)	5 (1.2%)
Withdrew Consent	3 (1.1%)	2 (1.4%)	5 (1.2%)
Lost to Follow-Up	4 (1.4%)	1 (0.7%)	5 (1.2%)
Pregnancy	0	1 (0.7%)	1 (0.2%)
Investigator's Discretion	1 (0.4%)	0	1 (0.2%)
Noncompliance with Study Drugs	0	1 (0.7%)	1 (0.2%)
Protocol Specified Criteria for Withdrawal	1 (0.4%)	0	1 (0.2%)
Death	0	0	0
Lack of Efficacy	0	0	0
Subjects Remaining on Study Up to the Data Cutoff Date	273 (95.8%)	133 (95.0%)	406 (95.5%)
Subjects Prematurely Discontinued Study Prior to the Data Cutoff Date	12 (4.2%)	7 (5.0%)	19 (4.5%)
Reasons for Prematurely Discontinued from Study			
Withdrew Consent	4 (1.4%)	2 (1.4%)	6 (1.4%)
Lost to Follow-Up	4 (1.4%)	1 (0.7%)	5 (1.2%)
Adverse Event	2 (0.7%)	2 (1.4%)	4 (0.9%)
Pregnancy	0	1 (0.7%)	1 (0.2%)
Investigator's Discretion	1 (0.4%)	0	1 (0.2%)
Non-Compliance with Study Drugs	0	1 (0.7%)	1 (0.2%)
Protocol Specified Criteria for Withdrawal	1 (0.4%)	0	1 (0.2%)
Death	0	0	0
Lack of Efficacy	0	0	0

a Of subjects who met all eligibility criteria and not randomized, 14 subjects were due to withdrawal of consent and 4 subjects were due to outside of visit window.

b Subjects randomized and never treated were due to withdrawal of consent.

The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

Case report form data collected up to 18 September 2015 and lab and dual-energy x-ray absorptiometry data collected up to 01 October 2015 are included in the Week 48 analysis data cut, including data collected after the Week 48 visit.

Source: Table 8-2 of the Clinical Study Report

There were a total of 914 patients screened and 426 (47%) were randomized 2:1 to the TAF and TDF treatment groups in Study GS-US-320-0108. All but one subject received at least one dose of study medication.

The majority of subjects in the study were still ongoing at the cut-off date for the primary analysis at Week 48. Only 4% of the subjects in the TAF treatment arm and 5% of the subjects in the TDF arm prematurely discontinued double-blind treatment and the same percentage discontinued from the study prior to the data cutoff date. The main reasons for discontinuation were withdrawal of consent, lost to follow-up and adverse events.

Table 3: Important Protocol Deviations (Study GS-US-320-0108, Safety Analysis Set)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	Total (N = 425)
Number of Subjects with at Least 1 Important Protocol Deviation	51 (17.9%)	30 (21.4%)	81 (19.1%)
Nonadherence of Study Drugs	14 (4.9%)	8 (5.7%)	22 (5.2%)
Overdose	3 (1.1%)	1 (0.7%)	4 (0.9%)
Procedural Violation	34 (11.9%)	22 (15.7%)	56 (13.2%)
Received Prohibited Concomitant Medications	2 (0.7%)	1 (0.7%)	3 (0.7%)
Violation of Inclusion/Exclusion Criteria	2 (0.7%)	0	2 (0.5%)

Source: Table 8-3 of the Clinical Study Report

Nineteen percent of the subjects in Study GS-US-320-0108 had at least one important protocol deviation the majority of which were procedural violations (13% overall) followed by nonadherence of study drugs (5% overall).

Table 4: Treatment Adherence (Study GS-US-320-0108, Safety Analysis Set)

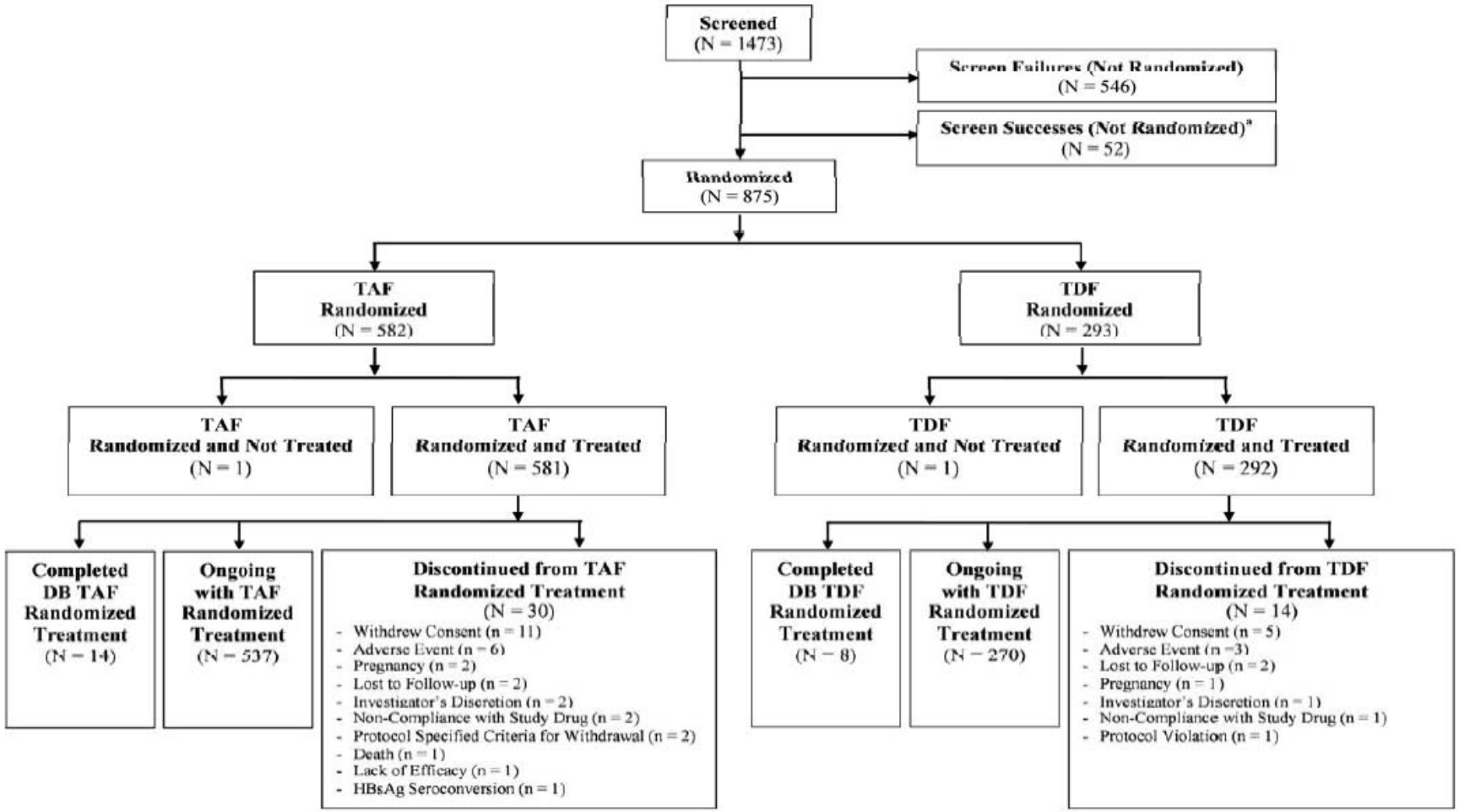
	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)
Number of Subjects Who Returned at Least 1 Bottle and Have Calculable Adherence	285 (100.0%)	140 (100.0%)
Study Drug Adherence Rate (%) Up to Week 48 Visit		
N	285	140
Mean (SD)	99.0 (1.27)	98.9 (1.59)
Median	99.5	99.6
Q1, Q3	98.7, 99.9	98.7, 99.8
Min, Max	90.9, 100.0	89.5, 100.0
Study Drug Adherence Rate Up to Week 48 Visit		
< 80%	0	0
≥ 80 to < 90%	0	1 (0.7%)
≥ 90 to < 95%	4 (1.4%)	5 (3.6%)
≥ 95%	281 (98.6%)	134 (95.7%)

Adherence was calculated based on pill count for the active drugs only.
Denominator for percentage of drug adherence category was the number of subjects who returned at least 1 bottle and had calculable drug adherence.

Source: Table 8-6 of the Clinical Study Report

Table 8-6 of the clinical study report is a summary of adherence to blinded study drugs. The median rate of adherence to active study drug, as measured by tablet counts, up to the Week 48 visit was 99.5% in the TAF group and 99.6% in the TDF treatment arm in Study GS-US-320-0108.

Figure 3: Disposition of Study Subjects (GS-US-320-0110)



DB = double blind

[a] For screen successes but not randomized, 34 were due to withdrawal of consent, 1 was due to investigator's discretion, 13 were due to outside of visit window, 1 was due to adverse event, 2 were due to other reasons, and 1 was due to lost to follow up.

No deaths occurred in any subject on treatment. Subject 09695-5212 discontinued study drugs and died 3 days after the last dose

Source: Figure 8-1 of the Clinical Study Report

Table 5: Subjects Screened, Enrolled, Treated: All Subjects (GS-US-320-0110, All Screened Subjects)

	TAF 25 mg	TDF 300 mg	Total
Subjects Screened			1473
Subjects Not Randomized			
Screen Failure Subjects Who Were Not Randomized			546
Subjects Met All Eligibility Criteria and Not Randomized[a]			52
Subjects in Randomized Analysis Set	582	293	875
Subjects Randomized and Never Treated[b]	1	1	2
Subjects in Safety Analysis Set	581	292	873
Subjects in Full Analysis Set (FAS)	581	292	873
Subjects Remaining on Double-Blind Study Treatment up to the Data-Cut Date	537 (92.4%)	270 (92.5%)	807 (92.4%)
Subjects Prematurely Discontinued Double-Blind Study Treatment prior to the Data-Cut Date	30 (5.2%)	14 (4.8%)	44 (5.0%)
Reasons for Prematurely Discontinued from Double-Blind Study Treatment			
Withdrew Consent	11 (1.9%)	5 (1.7%)	16 (1.8%)
Adverse Event	6 (1.0%)	3 (1.0%)	9 (1.0%)
Lost to Follow-Up	2 (0.3%)	2 (0.7%)	4 (0.5%)
Pregnancy	2 (0.3%)	1 (0.3%)	3 (0.3%)
Investigator's Discretion	2 (0.3%)	1 (0.3%)	3 (0.3%)
Non-Compliance with Study Drug	2 (0.3%)	1 (0.3%)	3 (0.3%)
Protocol Specified Criteria for Withdrawal	2 (0.3%)	0	2 (0.2%)
Death	1 (0.2%)[c]	0	1 (0.1%)[c]
Lack of Efficacy	1 (0.2%)	0	1 (0.1%)
Subjects Remaining on Study up to the Data-Cut Date	553 (95.2%)	278 (95.2%)	831 (95.2%)
Subjects Prematurely Discontinued Study prior to the Data-Cut Date	28 (4.8%)	14 (4.8%)	42 (4.8%)

	TAF 25 mg	TDF 300 mg	Total
Reasons for Prematurely Discontinued from Study			
Withdrew Consent	13 (2.2%)	7 (2.4%)	20 (2.3%)
Investigator's Discretion	5 (0.9%)	0	5 (0.6%)
Lost to Follow-Up	3 (0.5%)	2 (0.7%)	5 (0.6%)
Adverse Event	1 (0.2%)	2 (0.7%)	3 (0.3%)
Pregnancy	2 (0.3%)	1 (0.3%)	3 (0.3%)
Non-Compliance with Study Drug	1 (0.2%)	1 (0.3%)	2 (0.2%)
Death	1 (0.2%)	0	1 (0.1%)
Lack of Efficacy	1 (0.2%)	0	1 (0.1%)

[a] Of subjects who met all eligibility criteria and not randomized, 34 were due to withdrawal of consent, 1 was due to investigator's discretion, 13 were due to outside of visit window, 1 was due to adverse event, 2 were due to other reasons, and 1 was due to lost to follow-up.
[b] Subjects randomized and never treated were due to withdrawal of consent.
[c] No deaths occurred in any subject on treatment. Subject 09695-5212 discontinued study drugs and died 3 days after the last dose.
The denominator for percentages is based on the number of subjects in the safety analysis set.
CRF data collected up to 07 November 2015 and lab and DXA data collected up to 17 November 2015 are included in the Week 48 analysis data cutoff, including data collected after the Week 48 visit.
Source: Table 8-2 of the Clinical Study Report

There were a total of 1473 patients screened and 875 (59%) were randomized 2:1 to the TAF and TDF treatment groups in Study GS-US-320-0110. All but two subjects received at least one dose of study medication.

The majority of subjects in the study were still ongoing at the cut-off date for the primary analysis at Week 48. Only 5% of the subjects in each treatment arm prematurely discontinued double-blind treatment and the same percentage discontinued from the study prior to the data cutoff date. The main reason for discontinuation was withdrawal of consent.

Table 6: Important Protocol Deviations (Study GS-US-320-0110, Safety Analysis Set)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)
Number of Subjects with at Least 1 Important Protocol Deviation	140 (24.1%)	67 (22.9%)	207 (23.7%)
Incorrect Dispensing of Study Drugs	1 (0.2%)	2 (0.7%)	3 (0.3%)
Nonadherence of Study Drugs	25 (4.3%)	16 (5.5%)	41 (4.7%)
Overdose	18 (3.1%)	7 (2.4%)	25 (2.9%)
Procedural Violation	94 (16.2%)	43 (14.7%)	137 (15.7%)
Received Prohibited Concomitant Medications	7 (1.2%)	3 (1.0%)	10 (1.1%)
Violation of Inclusion/Exclusion Criteria	11 (1.9%)	5 (1.7%)	16 (1.8%)

Source: Table 8-3 of the Clinical Study Report

Twenty-four percent of the subjects in Study GS-US-320-0110 had at least one important protocol deviation the majority of which were procedural violations (16% overall) followed by nonadherence of study drugs (5% overall).

Table 7: Treatment Adherence (Study GS-US-320-0110, Safety Analysis Set)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)
Number of Subjects Who Returned at Least 1 Bottle and Have Calculable Adherence	581 (100.0%)	289 (99.0%)
Study Drug Adherence Rate (%) up to Week 48 Visit		
N	581	289
Mean (SD)	98.9 (1.52)	98.7 (1.57)
Median	99.4	99.3
Q1, Q3	98.5, 99.9	98.2, 99.7
Min, Max	89.5, 100.0	90.2, 100.0
Study Drug Adherence Rate up to Week 48 Visit		
< 80%	0	0
≥ 80 to < 90%	2 (0.3%)	0
≥ 90 to < 95%	14 (2.4%)	9 (3.1%)
≥ 95%	565 (97.2%)	280 (96.9%)

Adherence was calculated based on pill count for the active drugs only.
Denominator for percentage of drug adherence category was the number of subjects who returned at least 1 bottle and had calculable drug adherence.

Source: Table 8-6 of the Clinical Study Report

Table 8-6 of the clinical study report is a summary of adherence to blinded study drugs. The median rate of adherence to active study drug, as measured by tablet counts, up to the Week 48 visit was 99.4% in the TAF group and 99.3% in the TDF treatment arm in Study GS-US-320-0110.

3.2.3.2 Demographic and Baseline Characteristics

Table 8: Demographic and Baseline Characteristics (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	Total (N = 425)	TAF 25 mg vs TDF 300 mg P-Value[a]
Age (years)				
N	285	140	425	0.011
Mean (SD)	45 (11.6)	48 (10.4)	46 (11.3)	
Median	46	50	47	
Q1, Q3	37, 54	40, 56	37, 55	
Min, Max	19, 80	25, 72	19, 80	
Age Group (years)				
< 50	176 (61.8%)	69 (49.3%)	245 (57.6%)	0.015
≥ 50	109 (38.2%)	71 (50.7%)	180 (42.4%)	
Sex				
Male	173 (60.7%)	86 (61.4%)	259 (60.9%)	0.89
Female	112 (39.3%)	54 (38.6%)	166 (39.1%)	
Race				
Asian	205 (71.9%)	101 (72.1%)	306 (72.0%)	0.90
Black or African American	5 (1.8%)	3 (2.1%)	8 (1.9%)	
Native Hawaiian or Pacific Islander	2 (0.7%)	0	2 (0.5%)	
White	71 (24.9%)	35 (25.0%)	106 (24.9%)	
Other	2 (0.7%)	1 (0.7%)	3 (0.7%)	
Ethnicity				
Hispanic or Latino	2 (0.7%)	0	2 (0.5%)	0.23
Not Hispanic or Latino	279 (97.9%)	140 (100.0%)	419 (98.6%)	
Not Permitted	4 (1.4%)	0	4 (0.9%)	
Body Mass Index (kg/m^2)[b]				
N	285	140	425	0.45
Mean (SD)	24.6 (4.04)	24.9 (3.81)	24.7 (3.97)	
Median	24.3	24.4	24.3	
Q1, Q3	21.7, 27.0	22.1, 27.4	21.8, 27.3	
Min, Max	15.2, 39.3	16.6, 36.9	15.2, 39.3	

The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

a P-value was from the Cochran-Mantel-Haenszel test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively.

b Body Mass Index (BMI) = [Weight (kg) / Height $(m)^2$].

Source: Table 8-4 of the Clinical Study Report

With the exception of age, demographic characteristics in Study GS-US-320-0108 appeared to be fairly well balanced between the two treatment groups. Thirty-eight percent of the TAF treatment group compared to 51% of the TDF treatment group were 50 years of age and older. Thirty-nine percent of the subjects in both treatment arms were females, 72%% were Asian, 25% were white, only 2% were black or African American and <1% were Hispanic or Latino. The mean BMI was 25 kg/m^2 while the median BMI was 24 kg/m^2 in both treatment groups.

Table 9: Baseline Disease Characteristics (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	Total (N = 425)	TAF 25 mg vs TDF 300 mg P-Value[a]
HBV DNA (log_{10} IU/mL)				
N	285	140	425	0.63
Mean (SD)	5.7 (1.34)	5.8 (1.32)	5.8 (1.33)	
Median	5.6	5.7	5.7	
Q1, Q3	4.8, 6.7	5.0, 6.6	4.9, 6.7	
Min, Max	1.8, 9.9	1.4, 8.2	1.4, 9.9	
HBV DNA Categories				
< 7 log_{10} IU/mL	230 (80.7%)	116 (82.9%)	346 (81.4%)	0.69
≥ 7 log_{10} IU/mL - < 8 log_{10} IU/mL	42 (14.7%)	20 (14.3%)	62 (14.6%)	
≥ 8 log_{10} IU/mL	13 (4.6%)	4 (2.9%)	17 (4.0%)	
ALT (U/L)				
N	285	140	425	0.74
Mean (SD)	94 (88.3)	94 (80.8)	94 (85.8)	
Median	67	67	67	
Q1, Q3	44, 102	47, 102	45, 102	
Min, Max	17, 720	9, 491	9, 720	
ALT Level[b]				
≤ ULN	49 (17.2%)	19 (13.6%)	68 (16.0%)	0.77
> ULN - 5 × ULN	209 (73.3%)	109 (77.9%)	318 (74.8%)	
> 5 × ULN – 10 × ULN	22 (7.7%)	10 (7.1%)	32 (7.5%)	
> 10 × ULN	5 (1.8%)	2 (1.4%)	7 (1.6%)	
HBeAg Status[c]				
Positive	2 (0.7%)	2 (1.4%)	4 (0.9%)	0.47
Negative	283 (99.3%)	138 (98.6%)	421 (99.1%)	
HBV Genotype Group				
A	15 (5.3%)	6 (4.3%)	21 (4.9%)	0.13
B	60 (21.1%)	40 (28.6%)	100 (23.5%)	
C	115 (40.4%)	47 (33.6%)	162 (38.1%)	
D	90 (31.6%)	42 (30.0%)	132 (31.1%)	
E	5 (1.8%)	2 (1.4%)	7 (1.6%)	
H	0	2 (1.4%)	2 (0.5%)	
Unknown	0	1 (0.7%)	1 (0.2%)	

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	Total (N = 425)	TAF 25 mg vs TDF 300 mg P-Value[a]
Years Positive for HBV				
N	285	140	425	0.31
Mean (SD)	8.5 (7.85)	9.3 (8.72)	8.8 (8.14)	
Median	6.0	6.5	6.0	
Q1, Q3	2.0, 12.0	3.5, 11.0	3.0, 12.0	
Min, Max	1.0, 39.0	1.0, 49.0	1.0, 49.0	
Previous Oral Nucleoside/Nucleotide Treatment[d]				
Yes	60 (21.1%)	31 (22.1%)	91 (21.4%)	0.80
No	225 (78.9%)	109 (77.9%)	334 (78.6%)	
Cirrhosis History				
Yes	24 (11.0%)	14 (12.4%)	38 (11.4%)	0.70
No	195 (89.0%)	99 (87.6%)	294 (88.6%)	
Indeterminate/Unknown	66	27	93	
FibroTest Score				
N	280	139	419	0.60
Mean (SD)	0.43 (0.223)	0.45 (0.229)	0.44 (0.225)	
Median	0.41	0.42	0.42	
Q1, Q3	0.26, 0.58	0.27, 0.62	0.27, 0.59	
Min, Max	0.05, 0.97	0.04, 0.97	0.04, 0.97	
eGFR by CG (mL/min)				
N	285	140	425	0.13
Mean (SD)	104.7 (27.83)	100.3 (24.23)	103.2 (26.74)	
Median	99.6	98.4	98.5	
Q1, Q3	86.4, 120.6	83.2, 112.2	85.2, 117.6	
Min, Max	39.0, 214.2	59.4, 187.8	39.0, 214.2	
eGFR by CKD-EPI Creatinine (mL/min/1.73 m^2)				
N	285	140	425	0.040
Mean (SD)	99.8 (14.97)	96.7 (13.48)	98.8 (14.55)	
Median	100.9	97.1	99.4	
Q1, Q3	90.0, 109.6	87.5, 106.8	88.9, 108.7	
Min, Max	46.4, 132.9	53.5, 122.3	46.4, 132.9	

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	Total (N = 425)	TAF 25 mg vs TDF 300 mg P-Value[a]
eGFR by CKD-EPI Cystatin C (mL/min/1.73 m^2)[e]				
N	162	86	248	0.19
Mean (SD)	116.6 (13.00)	116.5 (25.45)	116.6 (18.25)	
Median	118.0	114.3	116.7	
Q1, Q3	109.1, 124.9	107.7, 124.8	108.2, 124.8	
Min, Max	64.8, 145.0	63.8, 308.6	63.8, 308.6	
Proteinuria by Urinalysis (Dipstick)				
Grade 0	270 (94.7%)	135 (96.4%)	405 (95.3%)	0.54
Grade 1	13 (4.6%)	5 (3.6%)	18 (4.2%)	
Grade 2	2 (0.7%)	0	2 (0.5%)	
Grade 3	0	0	0	
Diabetes Mellitus[f]				
Yes	26 (9.1%)	13 (9.3%)	39 (9.2%)	0.96
No	259 (90.9%)	127 (90.7%)	386 (90.8%)	
Cardiovascular Disease[f]				
Yes	11 (3.9%)	5 (3.6%)	16 (3.8%)	0.88
No	274 (96.1%)	135 (96.4%)	409 (96.2%)	
Hypertension[f]				
Yes	47 (16.5%)	33 (23.6%)	80 (18.8%)	0.080
No	238 (83.5%)	107 (76.4%)	345 (81.2%)	
Hyperlipidemia[f]				
Yes	33 (11.6%)	16 (11.4%)	49 (11.5%)	0.96
No	252 (88.4%)	124 (88.6%)	376 (88.5%)	

a P-value was from the Cochran-Mantel-Haenszel test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively.
b ULN based on central laboratory normal range.
c Four subjects changed HBeAg status from negative to positive at baseline from screening.
d Previous oral nucleoside/nucleotide treatment status was categorized by "Yes" or "No" irrespective of treatment duration.
e Cystatin C was not required for subjects enrolled prior to Amendment 2.
f Diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia were determined by medical history and/or concomitant medication.

Source: Table 8-5 of the Clinical Study Report

Baseline disease characteristics in Study GS-US-320-0108 appeared to be well balanced between the two treatment groups. The mean and median HBV DNA levels were nearly the same in both treatment arms (5.8 and 5.7 log10 IU/mL overall) while slightly more than 80% of the subjects in both arms had HBV DNA < 7 $\log_{10}$ IU/mL at baseline while only 5% of the TAF subjects and 3% of the TDF subjects had HBV DNA≥8 $\log_{10}$ IU/mL.

A similar proportion of subjects in each treatment group had baseline ALT above the ULN based on the central laboratory normal range (TAF 83%; TDF 86%). Although HBeAg negative and anti-HBe positive at screening, 4 subjects (TAF 0.7%, 2 subjects; TDF 1.4%, 2 subjects) were HBeAg positive (including 1 subject who was borderline) at their baseline visit. These 4 subjects were included in the FAS.

The percentage of subjects with each HBV genotype was similar between treatment groups. The most common baseline HBV genotypes in both treatment groups were genotype C (38%), genotype D (31%), and genotype B (24%); 5% were genotype A. There were few subjects (< 2% in either treatment group) with baseline genotype E, H, or unknown.

At baseline, 11% of subjects in the TAF group and 12% of subjects in the TDF group reported a history of cirrhosis; 11% of subjects in the TAF group and 14% of subjects in the TDF group had a FibroTest score of ≥0.75 (from table 6 in Section 15.1 of the Clinical Study Report),, which was suggestive of cirrhosis (i.e., equivalent to a Metavir score F4). A total of 48 subjects (11%) had prior exposure to interferons (TAF 10%, 29 subjects; TDF 14%, 19 subjects) (Section 15.1, Table 8 of the Clinical Study Report). A similar percentage of subjects (21% overall) in each treatment group were treated previously with oral antivirals (OAVs). At baseline, the median $eGFR_{CG}$ value was 99.6 mL/min in the TAF group compared with 98.4 mL/min in the TDF group.

Table 10: Analysis Sets at Week 48 (Randomized Analysis Set) (Study GS-US-320-0108)

	TAF 25 mg	TDF 300 mg	Total
Subjects in Randomized Analysis Set	285	141	426
Subjects in Safety Analysis Set	285 (100.0%)	140 (99.3%)	425 (99.8%)
Subjects in Full Analysis Set (FAS)	285 (100.0%)	140 (99.3%)	425 (99.8%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	272 (95.4%)	128 (90.8%)	400 (93.9%)

Exclusion criteria from PP Analysis Sets were only applicable to the FAS subjects. A subject may have fit more than 1 exclusion criterion from the PP Analysis Sets.

Source: Table 8-7 of the Clinical Study Report

Overall, 425 subjects (TAF 285 subjects; TDF 140 subjects) who were randomized and received at least 1 dose of treatment were included in both the Safety Analysis Set and in the FAS for the Week 48 analysis. A total of 25 subjects (TAF 13 subjects; TDF 12 subjects) were excluded from the Week 48 PP Analysis Set. According to the applicant, of the 13 subjects in the TAF group excluded from the PP Analysis Set, 10 subjects did not have on-treatment HBV DNA values available at Week 48 due to missing value (n = 1) or discontinuation from study for reasons other than lack of efficacy (n = 9), while 3 subjects were excluded for having an adherence rate for the active study drug below the 2.5th percentile.

Table 11: Demographic and Baseline Characteristics (Study GS-US-320-0110) (Safety Analysis Set)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs TDF 300 mg P-Value[a]
Age (Years)				
N	581	292	873	0.74
Mean (SD)	38 (11.0)	38 (11.7)	38 (11.3)	
Median	37	36	36	
Q1, Q3	29, 45	30, 47	29, 46	
Min, Max	18, 69	18, 68	18, 69	
Age Group (Years)				
< 50	493 (84.9%)	234 (80.1%)	727 (83.3%)	0.078
≥ 50	88 (15.1%)	58 (19.9%)	146 (16.7%)	
Sex				
Male	371 (63.9%)	189 (64.7%)	560 (64.1%)	0.80
Female	210 (36.1%)	103 (35.3%)	313 (35.9%)	
Race				
Asian	482 (83.0%)	232 (79.5%)	714 (81.8%)	0.12
Black or African American	2 (0.3%)	3 (1.0%)	5 (0.6%)	
Native Hawaiian or Pacific Islander	1 (0.2%)	3 (1.0%)	4 (0.5%)	
White	96 (16.5%)	53 (18.2%)	149 (17.1%)	
Other	0	1 (0.3%)	1 (0.1%)	
Ethnicity				
Hispanic or Latino	4 (0.7%)	2 (0.7%)	6 (0.7%)	0.82
Not Hispanic or Latino	573 (98.6%)	289 (99.0%)	862 (98.7%)	
Not Permitted	4 (0.7%)	1 (0.3%)	5 (0.6%)	

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs TDF 300 mg P-Value[a]
Body Mass Index (kg/m^2)[b]				
N	581	292	873	0.16
Mean (SD)	23.8 (4.14)	24.1 (4.00)	23.9 (4.10)	
Median	23.5	23.8	23.6	
Q1, Q3	20.8, 26.1	21.5, 26.3	21.0, 26.2	
Min, Max	14.4, 44.5	16.7, 38.4	14.4, 44.5	

a P-value was from the CMH test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively.
b Body Mass Index (BMI) = [Weight (kg) / Height (m^2)].
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.
Source: Table 8-4 of the Clinical Study Report

Demographic characteristics in Study GS-US-320-0110 appeared to be fairly well balanced between the two treatment groups. Fifteen percent of the TAF treatment group compared to 20% of the TDF treatment group were 50 years of age and older. Overall 36% of the subjects were females, 82%% were Asian, 17% were white, <1% were black or African American and <1% were Hispanic or Latino. The mean and median BMI were 24 kg/m^2 in both treatment groups.

Table 12: Baseline Disease Characteristics (Study GS-US-320-0110)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs. TDF 300 mg P-Value[a]
HBV DNA (log_{10} IU/mL)				
N	581	292	873	0.51
Mean (SD)	7.6 (1.34)	7.6 (1.41)	7.6 (1.36)	
Median	7.9	8.0	7.9	
Q1, Q3	6.9, 8.5	6.8, 8.6	6.9, 8.6	
Min, Max	2.5, 9.9	2.6, 9.9	2.5, 9.9	
HBV DNA Categories				
< 8 log_{10} IU/mL	309 (53.2%)	150 (51.4%)	459 (52.6%)	0.61
≥ 8 log_{10} IU/mL	272 (46.8%)	142 (48.6%)	414 (47.4%)	
ALT (U/L)				
N	581	292	873	0.64
Mean (SD)	117 (105.1)	125 (128.2)	120 (113.4)	
Median	85	86	85	
Q1, Q3	61, 139	57, 137	60, 138	
Min, Max	13, 1160	21, 872	13, 1160	
ALT Level[b]				
≤ ULN	44 (7.6%)	24 (8.2%)	68 (7.8%)	0.16
> ULN – 5 × ULN	470 (80.9%)	225 (77.1%)	695 (79.6%)	
> 5 × ULN - 10 × ULN	56 (9.6%)	30 (10.3%)	86 (9.9%)	
> 10 × ULN	11 (1.9%)	13 (4.5%)	24 (2.7%)	
HBeAg Status[c]				
Positive	567 (97.6%)	288 (98.6%)	855 (97.9%)	0.31
Negative	14 (2.4%)	4 (1.4%)	18 (2.1%)	

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs. TDF 300 mg P-Value[a]
HBV Genotype Group				
A	39 (6.7%)	25 (8.6%)	64 (7.3%)	0.78
B	100 (17.2%)	48 (16.4%)	148 (17.0%)	
C	303 (52.2%)	152 (52.1%)	455 (52.1%)	
D	134 (23.1%)	63 (21.6%)	197 (22.6%)	
E	2 (0.3%)	1 (0.3%)	3 (0.3%)	
F	3 (0.5%)	2 (0.7%)	5 (0.6%)	
Unknown	0	1 (0.3%)	1 (0.1%)	
Years Positive for HBV				
N	579	290	869	0.80
Mean (SD)	6.3 (6.24)	6.3 (6.33)	6.3 (6.27)	
Median	4.0	4.0	4.0	
Q1, Q3	2.0, 8.0	2.0, 8.0	2.0, 8.0	
Min, Max	1.0, 43.0	0.0, 36.0	0.0, 43.0	
Previous Oral Nucleoside/Nucleotide Treatment[d]				
Yes	151 (26.0%)	77 (26.4%)	228 (26.1%)	0.90
No	430 (74.0%)	215 (73.6%)	645 (73.9%)	
Cirrhosis History				
Yes	41 (9.8%)	24 (11.3%)	65 (10.3%)	0.58
No	376 (90.2%)	189 (88.7%)	565 (89.7%)	
Indeterminate/Unknown	164	79	243	
FibroTest Score				
N	566	282	848	0.20
Mean (SD)	0.34 (0.227)	0.32 (0.225)	0.34 (0.227)	
Median	0.29	0.25	0.27	
Q1, Q3	0.16, 0.48	0.14, 0.47	0.15, 0.48	
Min, Max	0.04, 0.98	0.03, 0.99	0.03, 0.99	

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs. TDF 300 mg P-Value[a]
eGFR by CG (mL/min)				
N	581	292	873	0.53
Mean (SD)	113.7 (27.78)	112.5 (29.33)	113.3 (28.29)	
Median	108.6	109.2	109.2	
Q1, Q3	94.9, 128.4	93.0, 128.7	94.4, 128.4	
Min, Max	54.6, 235.8	39.6, 227.4	39.6, 235.8	
eGFR by CKD-EPI Creatinine (mL/min/1.73m^2)				
N	581	292	873	0.25
Mean (SD)	107.8 (14.57)	106.4 (15.10)	107.3 (14.76)	
Median	109.0	108.6	109.0	
Q1, Q3	99.3, 118.0	97.0, 117.0	98.5, 117.7	
Min, Max	45.4, 140.9	38.0, 136.8	38.0, 140.9	
eGFR by CKD-EPI Cystatin C (mL/min/1.73 m^2)[e]				
N	327	162	489	0.69
Mean (SD)	121.4 (12.82)	120.5 (14.90)	121.1 (13.54)	
Median	121.4	121.9	121.8	
Q1, Q3	114.3, 129.9	112.9, 130.0	113.7, 129.9	
Min, Max	64.1, 158.4	45.2, 162.7	45.2, 162.7	
Proteinuria by Urinalysis (Dipstick)				
Grade 0	538 (92.6%)	259 (88.7%)	797 (91.3%)	0.15
Grade 1	40 (6.9%)	31 (10.6%)	71 (8.1%)	
Grade 2	3 (0.5%)	2 (0.7%)	5 (0.6%)	
Grade 3	0	0	0	
Diabetes Mellitus[f]				
Yes	30 (5.2%)	16 (5.5%)	46 (5.3%)	0.84
No	551 (94.8%)	276 (94.5%)	827 (94.7%)	
Cardiovascular Disease[f]				
Yes	17 (2.9%)	9 (3.1%)	26 (3.0%)	0.90
No	564 (97.1%)	283 (96.9%)	847 (97.0%)	

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	Total (N = 873)	TAF 25 mg vs. TDF 300 mg P-Value[a]
Hypertension[f]				
Yes	51 (8.8%)	29 (9.9%)	80 (9.2%)	0.58
No	530 (91.2%)	263 (90.1%)	793 (90.8%)	
Hyperlipidemia[f]				
Yes	42 (7.2%)	25 (8.6%)	67 (7.7%)	0.49
No	539 (92.8%)	267 (91.4%)	806 (92.3%)	

a P-value was from the Cochran-Mantel-Haenszel test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively.
b ULN based on central laboratory normal range.
c Eighteen subjects changed HBeAg status from positive to negative at baseline from screening.
d Previous oral nucleoside/nucleotide treatment status was categorized by 'Yes' or 'No' irrespective of treatment duration.
e Cystatin C was not required for subjects enrolled prior to Amendment 2.
f Diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia were determined by medical history and/or concomitant medication.

Source: Table 8-5 of the Clinical Study Report

Baseline disease characteristics in Study GS-US-320-0110 appeared to be well balanced between the two treatment groups. The mean and median HBV DNA levels were nearly the same in both treatment arms (7.6 and 7.9 log10 IU/mL overall) while slightly less than 50% of the subjects in both arms had HBV DNA ≥8 $\log_{10}$ IU/mL at baseline.

The same proportion of subjects in each treatment group had baseline ALT above the ULN based on the central laboratory normal range (92%) while 13% of the subjects had ALT>5 × ULN at baseline. Although HBeAg positive and anti-HBe positive at screening, 18 subjects (TAF 2.4%, 14 subjects; TDF 1.4%, 4 subjects) were HBeAg negative at their baseline visit. All 18 of these subjects were included in the FAS.

The percentage of subjects with each HBV genotype was similar between treatment groups. The most common baseline HBV genotypes in both treatment groups were genotype C (52%), genotype D (23%), and genotype B (17%); 7% were genotype A. There were few subjects (1% overall) with baseline genotype E, H, or unknown.

At baseline, 10% of subjects in the TAF group and 11% of subjects in the TDF group reported a history of cirrhosis; 11% of subjects in the TAF group and 8% of subjects in each treatment group had a FibroTest score of ≥0.75 (from table 6 in Section 15.1 of the Clinical Study Report), which was suggestive of cirrhosis (i.e., equivalent to a Metavir score F4).

A total of 106 subjects (12%) had prior exposure to interferons (TAF 13%; TDF 10%) (Section 15.1, Table 8 of the Clinical Study Report) while 26% of the subjects in each treatment group received prior OAVs. At baseline, the median $eGFR_{CG}$ value was 109 mL/min in each treatment group.

Table 13: Analysis Sets (Randomized Analysis Set) (Study GS-US-320-0110)

	TAF 25 mg	TDF 300 mg	Total
Subjects in Randomized Analysis Set	582	293	875
Subjects in Safety Analysis Set	581 (99.8%)	292 (99.7%)	873 (99.8%)
Subjects in Full Analysis Set (FAS)	581 (99.8%)	292 (99.7%)	873 (99.8%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	544 (93.5%)	274 (93.5%)	818 (93.5%)

Exclusion criteria from PP Analysis Sets were only applicable to the FAS subjects. A subject may fit more than 1 exclusion criterion from the PP Analysis Sets.

Source: Table 8-7 of the Clinical Study Report

Overall, 873 subjects (TAF 581 subjects; TDF 292 subjects) who were randomized and received at least 1 dose of treatment were included in both the Safety Analysis Set and in the FAS for the Week 48 analysis. A total of 55 subjects (TAF 37 subjects; TDF 18 subjects) were excluded from the Week 48 PP Analysis Set. According to the applicant, of the 37 subjects in the TAF group excluded from the PP Analysis Set, 26 subjects did not have on-treatment HBV DNA values available at Week 48 due to missing value (n=1) or discontinuation from study for reasons other than lack of efficacy (n=25), while 12 subjects were excluded for having an adherence rate for the active study drug below the 2.5th percentile.

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Analyses

Table 14: Summary of Primary Efficacy Analysis (Percentage of subjects with HBV DNA <29 IU/mL at Week 48 for Study GS-US-320-0108)

Treatment Arm	TAF 25 mg	TDF 300 mg
	n/N %	n/N %
Number and Percentage of Responders	268/285 94.0%	130/140 92.9%
Risk Difference and exact 95% CI (TAF – TDF)	+1.2% (-3.5% to +7.3%) p=0.68	
Risk Difference and 95% CI adjusted for baseline strata	+1.7% (-3.5% to +7.1%) p=0.51	

NI Margin= -10%
Source: Reviewer's Analysis

The reviewer compared the percentage of subjects with virologic responses at Week 48 (HBV DNA <29 IU/mL) based on the full analysis set and was able to replicate the applicant's analyses for Study GS-US-320-0108. In the TAF 25 mg arm, 94% (268/285) of the patients achieved virologic response compared to 93% (130/140) in the TDF 300 mg arm. The unweighted difference was +1.2% with a 95% CI of (-3.5% to +7.3%) while the adjusted difference was +1.7% with a 95% CI of (-3.5% to +7.1%), both in favor of TAF.

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Table 15: Applicant's Summary of HBV DNA Outcome at Week 48 Using HBV DNA of < 29 IU/mL, Missing = Failure (Study GS-US-320-0108)

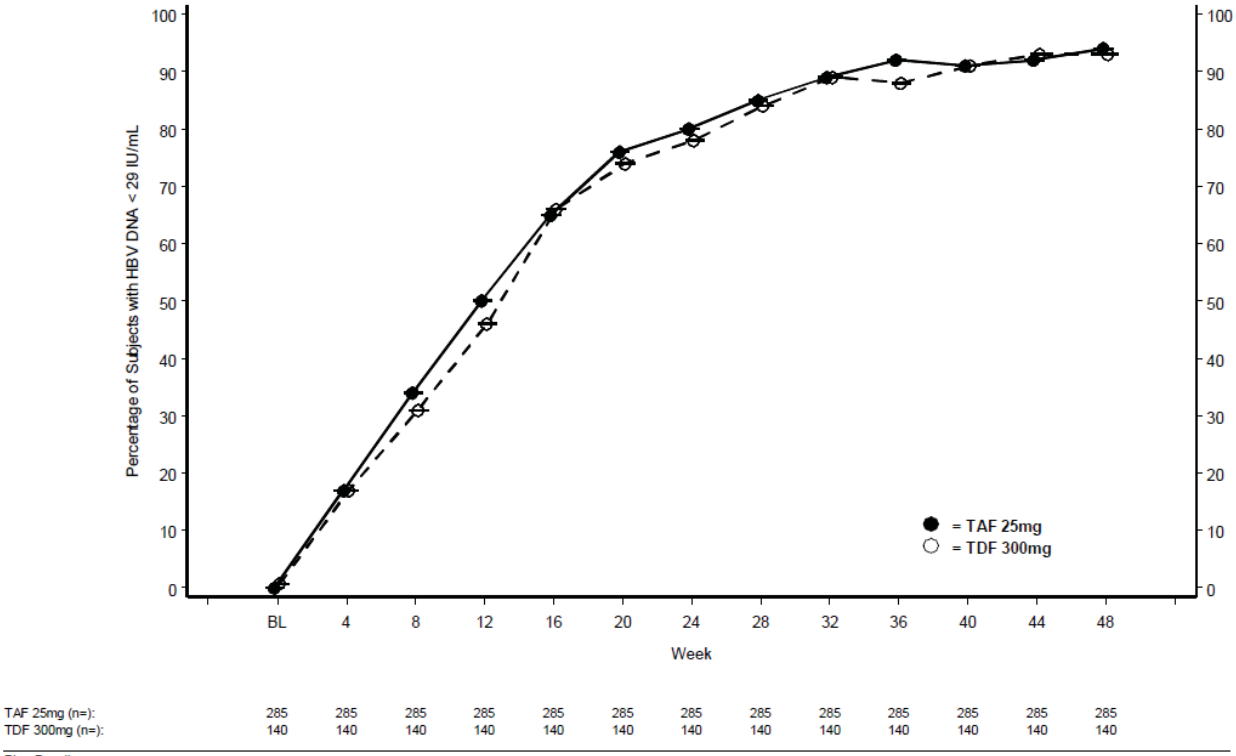
	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
Success				
HBV DNA < 29 IU/mL	268 (94.0%)	130 (92.9%)	0.47	1.8% (−3.6% to 7.2%)
Failure				
HBV DNA ≥ 29 IU/mL	7 (2.5%)	4 (2.9%)		
Discontinued Study Drugs Due to Lack of Efficacy	0	0		
Discontinued Study Drugs Due to AE/Death	3 (1.1%)	1 (0.7%)		
Discontinued Study Drugs Due to Other Reasons[c]	6 (2.1%)	4 (2.9%)		
Missing Data During Window but on Study Drugs	1 (0.4%)	1 (0.7%)		

Prop Diff = difference in proportions
The Week 48 window was between Days 322 and 363 (inclusive).
a P-value for the superiority test comparing the percentages of HBV DNA < 29 IU/mL was from the Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drugs due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drugs, protocol violation, pregnancy, and study termination by sponsor.

Source: Table 9-1 of the Clinical Study Report

In the applicant's analysis the adjusted difference was +1.8% with a 95% CI of (-3.6% to +7.2%). Because the lower bound of the 2-sided 95% CI of the difference (TAF – TDF) in the response rate was greater than the pre-specified −10% margin, the applicant concluded that the TAF group met the primary endpoint of noninferiority to the TDF group. Reasons for discontinuation included AE/death (1% for TAF, <1% for TDF), missing data during window but on study drugs (<1% in each treatment group) and other reasons (2% for TAF, 3% for TDF).

Figure 4: Percentage of Subjects with Plasma HBV DNA< 29 IU/mL by Visit, Missing = Failure (Study GS-US-320-0108)



Source: Figure 9-1 of the Clinical Study Report

The kinetics of HBV DNA decline as assessed by the proportion of subjects with HBV DNA < 29 IU/mL over 48 weeks were similar in the two treatment groups in Study GS-US-320-0108.

Table 16: Summary of Primary Efficacy Analysis Percentage of subjects with HBV DNA <29 IU/mL at Week 48 Study GS-US-320-0110

Treatment Arm	TAF 25 mg	TDF 300 mg
	n/N %	n/N %
Number and Percentage of Responders	371/581 63.9%	195/292 66.8%
Risk Difference and exact 95% CI (TAF – TDF)	-2.9% (-9.5% to +3.85%) p=0.40	
Risk Difference and 95% CI adjusted for baseline strata	-3.5% (-9.7% to +2.6%) p=0.26	

NI Margin= -10%
Source: Reviewer's Analysis

The reviewer compared the percentage of subjects with virologic responses at Week 48 (HBV DNA <29 IU/mL) based on the full analysis set and was able to replicate the applicant's analyses for Study GS-US-320-0110. In the TAF 25 mg arm, 64% (371/581) of the patients achieved virologic response compared to 67% (195/295) in the TDF 300 mg arm. The unweighted difference was -2.9% with a 95% CI of (-9.5% to +3.85%) while the adjusted difference was -3.5% with a 95% CI of (-9.7% to +2.6%), both in favor of TDF.

Table 17: Applicant's Summary of GS-US-320-0110: HBV DNA Outcome at Week 48 Using HBV DNA Cutoff at < 29 IU/mL, Missing = Failure (Full Analysis Set)

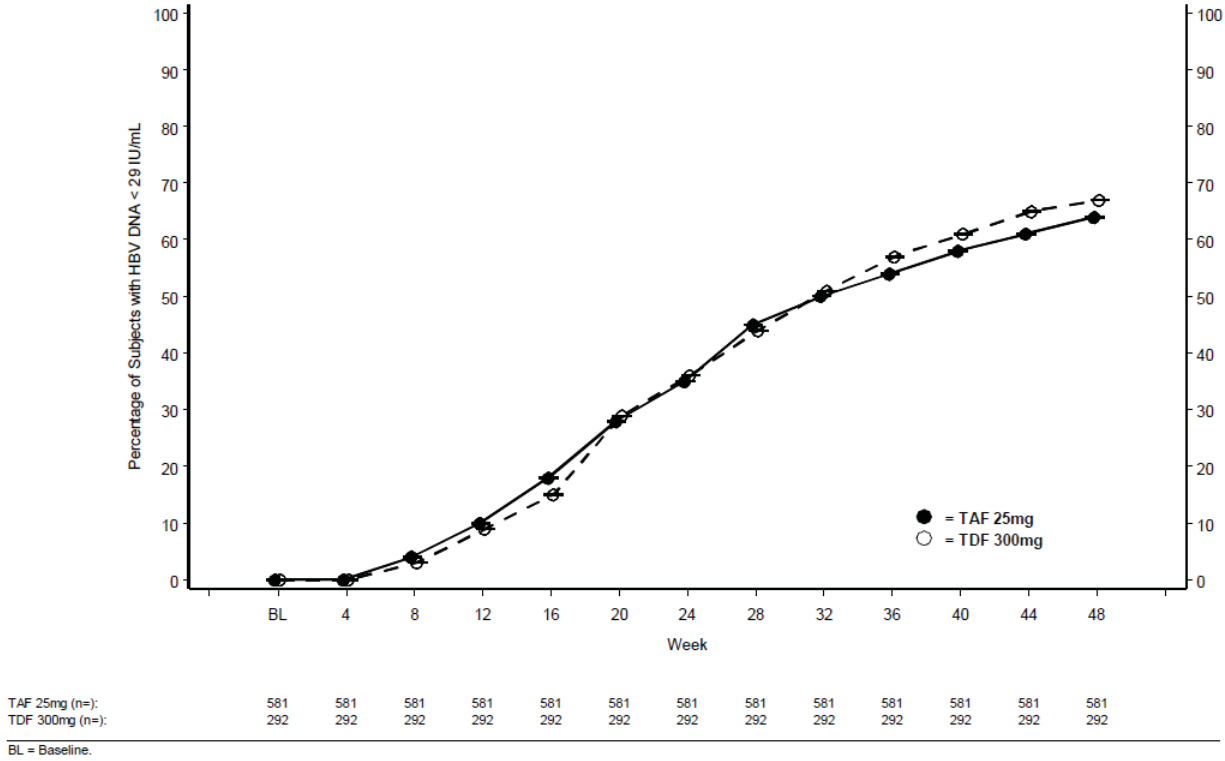
	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
Success				
HBV DNA < 29 IU/mL	371 (63.9%)	195 (66.8%)	0.25	−3.6% (−9.8% to 2.6%)
Failure				
HBV DNA ≥ 29 IU/mL	183 (31.5%)	88 (30.1%)		
Discontinued Study Drug Due to Lack of Efficacy	1 (0.2%)	0		
Discontinued Study Drug Due to AE/Death[c]	6 (1.0%)	3 (1.0%)		
Discontinued Study Drug Due to Other Reasons[d]	19 (3.3%)	6 (2.1%)		
Missing Data During Window but on Study Drug	1 (0.2%)	0		

Prop Diff = difference in proportions
The Week 48 window was between Day 322 and 363 (inclusive).
a P-value for the superiority test comparing the percentages of HBV DNA < 29 IU/mL was from the Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
c No deaths occurred in any subject on treatment. Subject 09695-5212 discontinued study drugs and died 3 days after the last dose (Appendix 16.2, Listing 22). After the database was closed, the investigator clarified that the subject discontinued due to coma.
d Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, and pregnancy.

Source: Table 9-1 of the Clinical Study Report

In the applicant's analysis the adjusted difference was -3.6% with a 95% CI of (-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 pre-specified −10% margin, the applicant concluded that the TAF group met the primary endpoint of noninferiority to the TDF group. Reasons for discontinuation included AE/death (1% for TAF and TDF), missing data during window but on study drugs (<1% for TAF, 0% for TDF) and other reasons (3% for TAF, 2% for TDF).

Figure 5: Percentage of Subjects with Plasma HBV DNA< 29 IU/mL by Visit, Missing = Failure (Study GS-US-320-0110)



Source: Figure 9-1 of the Clinical Study Report

The kinetics of HBV DNA decline as assessed by the proportion of subjects with HBV DNA < 29 IU/mL over 48 weeks were similar in the two treatment groups in Study GS-US-320-0110. However after 32 weeks the percentage of responders for TAF was numerically higher than TDF.

3.2.4.2 Analysis of Selected Secondary Efficacy Endpoints

Table 18: Percentage of Subjects with HBV DNA < 29 IU/mL (Target Not Detected, Target Detected) at Week 48, Missing = Failure (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
HBV DNA at Week 48				
< 29 IU/mL	268/285 (94.0%)	130/140 (92.9%)	0.47	1.8% (−3.6% to 7.2%)
95% CI	90.6% to 96.5%	87.3% to 96.5%		
< 29 IU/mL Target Not Detected	60/285 (21.1%)	24/140 (17.1%)		
< 29 IU/mL Target Detected	208/285 (73.0%)	106/140 (75.7%)		

Prop Diff = difference in proportions
The denominator for percentages is based on the number of subjects in the Full Analysis Set.
P-value, proportion difference, and 95% CI were based on a dichotomized response: success (HBV DNA < 29 IU/mL) or failure (HBV DNA ≥ 29 IU/mL or missing).

a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.

b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-2 of the Clinical Study Report

The applicant noted that the proportion of subjects with HBV DNA < 29 IU/mL (target not detected) is reflective of complete viral suppression and that the proportion of responders for this endpoint was numerically higher for TAF than for TDF (21% vs. 17%).

Table 19: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48, Missing = Excluded (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
HBV DNA at Week 48				
< 29 IU/mL	268/275 (97.5%)	130/134 (97.0%)	0.46	1.2% (−2.8% to 5.1%)
95% CI	94.8% to 99.0%	92.5% to 99.2%		
< 29 IU/mL Target Not Detected	60/275 (21.8%)	24/134 (17.9%)		
< 29 IU/mL Target Detected	208/275 (75.6%)	106/134 (79.1%)		

Prop Diff = difference in proportions
The denominator for percentage is the number of subjects in the full analysis set with nonmissing HBV DNA value at each visit.
P-value, proportion difference, and 95% CI were based on a dichotomized response: success (HBV DNA < 29 IU/mL) or failure (HBV DNA ≥ 29 IU/mL or missing).

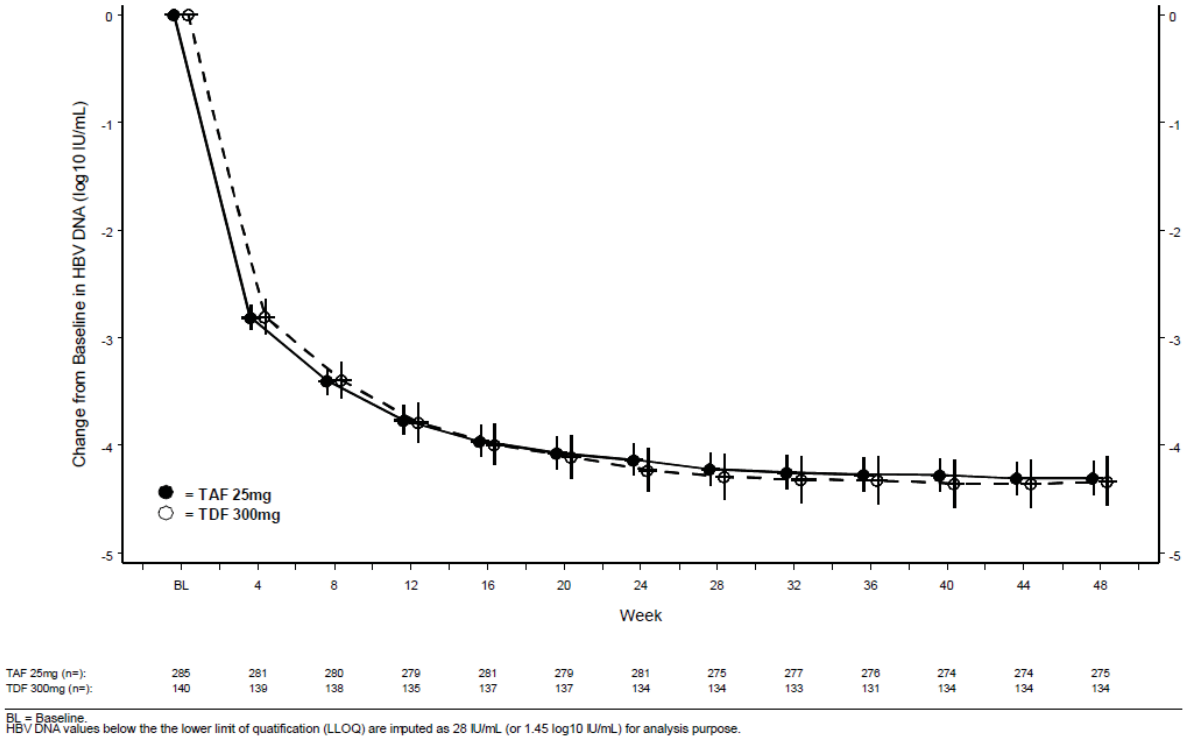
a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.

b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-3 of the Clinical Study Report

Compared to the primary efficacy analysis that assumed patients who were missing to be failures (M=F) slightly higher response rates were observed for the primary efficacy endpoint in both treatment arms using the missing=excluded imputation (97.5% for TAF and 97.0% for TDF) but the difference between both treatment groups didn't change enough to affect the conclusion of NI. The proportion of subjects with HBV DNA < 29 IU/mL (target not detected) was numerically higher for TAF than for TDF (22% vs. 18%).

Figure 6: Mean and 95% CIs of Change from Baseline in HBV DNA (log10 IU/mL) by Visit (Observed Data) (Study GS-US-320-0108)



Source: Figure 9-2 of the Clinical Study Report

Similar patterns were observed in both treatment arms for mean changes from baseline for Study GS-US-320-0108. As can be seen in Figure 9-2 of the Clinical Study Report all of the 95% confidence intervals overlapped. (However these results were based on observed data so the effect of the relatively small amount of missing data was not accounted for.)

Table 20: Percentage of Subjects with Normalized ALT at Week 48, Missing = Failure (Study GS-US-320-0108, Full Analysis Set)

	TAF 25 mg	TDF 300 mg	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
Normalized ALT (Central Laboratory)				
Week 48	196/236 (83.1%)	91/121 (75.2%)	0.076	8.0% (−1.3% to 17.2%)
Normalized ALT (AASLD)				
Week 48	137/276 (49.6%)	44/138 (31.9%)	< 0.001	17.9% (8.0% to 27.7%)

AASLD = American Association for the Study of Liver Disease; Prop Diff = difference in proportions

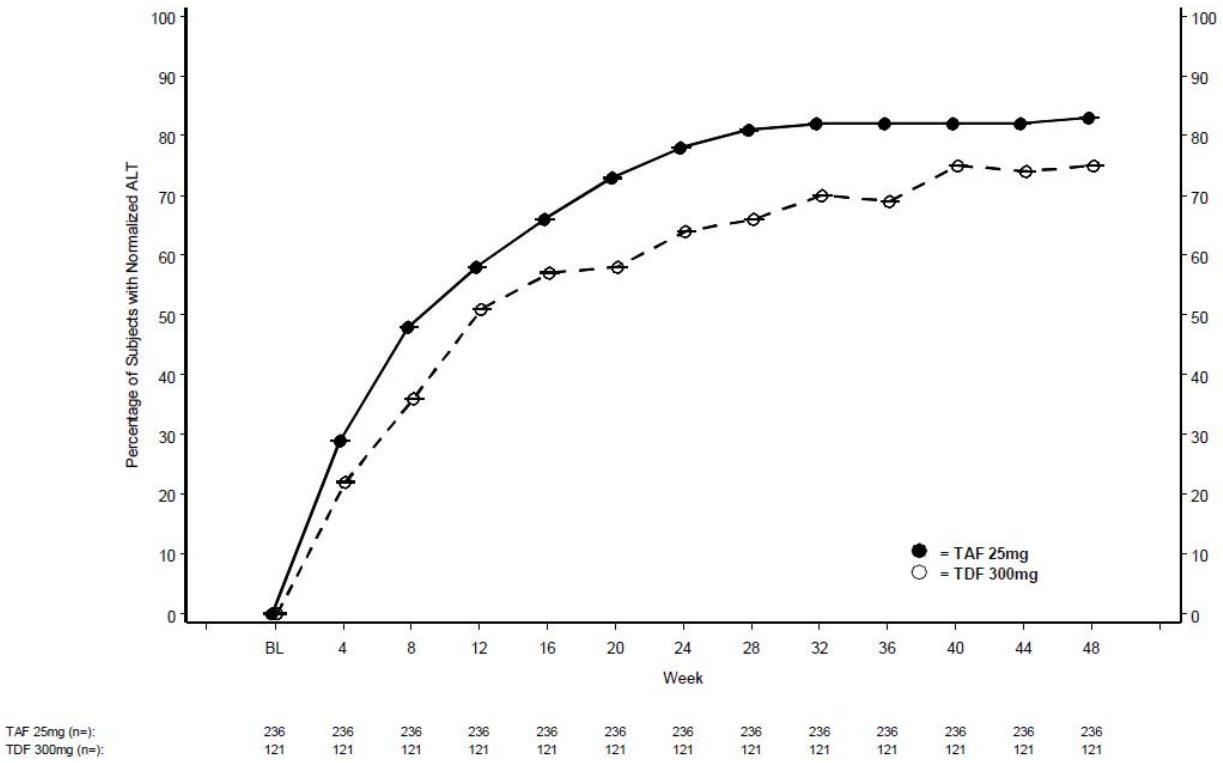
a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.

b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-4 of the Clinical Study Report

Using the central laboratory criteria, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) was numerically higher for the TAF group (83%) compared to the TDF group (75%) (p=0.076). Using the AASLD criteria (≤30 U/L for men and ≤19 U/L for women), the percentage of subjects with normalized ALT was significantly higher in the TAF group (50%) than in the TDF group (32%) (p<0.001) at Week 48 using the M = F method.

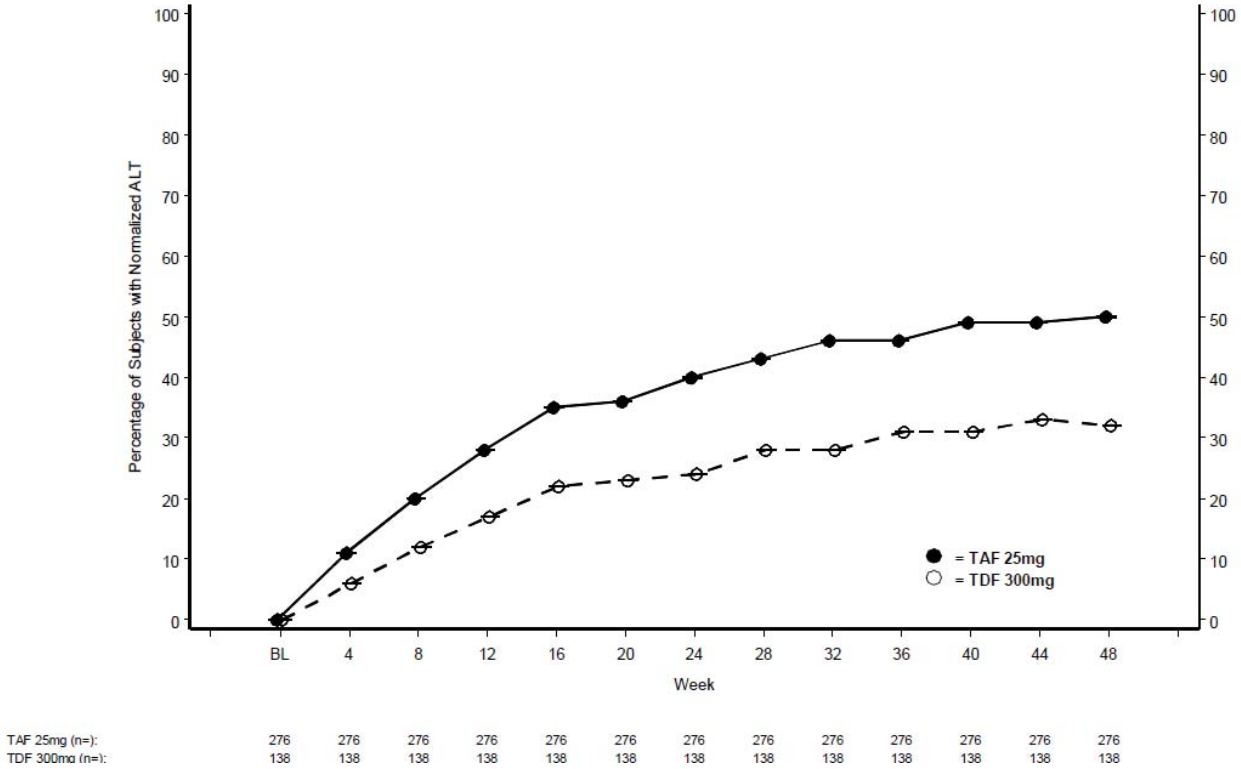
Figure 7: Percentage of Subjects with ALT Normalization by Visit, Missing = Failure (Central Laboratory Criteria) (Study GS-US-320-0108, Full Analysis Set)



Source: Figure 9-3 of the Clinical Study Report

Using the central laboratory criteria, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 4 through 48.

Figure 8: Percentage of Subjects with ALT Normalization by Visit, Missing = Failure (AASLD Criteria) (Study GS-US-320-0108, Full Analysis Set)



Source: Figure 9-4 of the Clinical Study Report

Response rates at each post-baseline visit using AASLD criteria for both treatment arms were lower than they were using Central Laboratory criteria. According to the applicant, the percentage of subjects with normalized ALT using the AASLD criteria was significantly higher in the TAF group than in the TDF group at all time-points from Week 8 onward using the M = F method.

Table 21: FibroTest Score and Change from Baseline in FibroTest Score by Visit (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg	
			P-Value	Diff in LSMs (95% CI)
Baseline				
N	280	139	0.53	−0.01 (−0.06 to 0.03)
Mean (SD)	0.43 (0.223)	0.45 (0.229)		
95% CI	(0.41 , 0.46)	(0.41 , 0.49)		
Median	0.41	0.42		
Q1, Q3	0.26, 0.58	0.27, 0.62		
Min, Max	0.05, 0.97	0.04, 0.97		
At Week 48				
N	275	135		
Mean (SD)	0.38 (0.213)	0.42 (0.212)		
95% CI	(0.35 , 0.40)	(0.39 , 0.46)		
Median	0.35	0.38		
Q1, Q3	0.20, 0.51	0.25, 0.60		
Min, Max	0.00, 0.97	0.05, 0.89		
Change at Week 48				
N	271	134	0.028	−0.03 (−0.05 to 0.00)
Mean (SD)	−0.05 (0.108)	−0.03 (0.131)		
95% CI	(−0.07 , −0.04)	(−0.05 , 0.00)		
Median	−0.04	−0.01		
Q1, Q3	−0.12, 0.01	−0.09, 0.05		
Min, Max	−0.40, 0.23	−0.61, 0.26		

Diff = difference; LSM = least-squares mean
P-value, difference in least-squares means, and its 95% CI were from ANOVA model with baseline HBV DNA categories, oral antiviral treatment status, and treatment group as fixed effects in the model.

Source: Table 9-5 of the Clinical Study Report

Table 9–5 in the Clinical Study Report presents the change from baseline in FibroTest scores for the FAS. At Week 48, the mean (SD) change from baseline in FibroTest scores in the TAF group was −0.05 (0.11) and in the TDF group was −0.03 (0.13) (least-squares means [LSM] difference: −0.03, 95% CI: −0.05 to 0.00; p = 0.028).

Table 22: Shift Table of Fibrosis Stage by FibroTest by Visit (Study GS-US-320-0108)

	TAF 25 mg (N = 285) Baseline				TDF 300 mg (N = 140) Baseline			
	0.00-0.48 (N = 169)	0.49-0.74 (N = 80)	0.75-1.00 (N = 31)	Missing (N = 5)	0.00-0.48 (N = 84)	0.49-0.74 (N = 35)	0.75-1.00 (N = 20)	Missing (N = 1)
At Week 48								
0.00-0.48	155 (93.9%)	32 (41.6%)	2 (6.9%)	4	76 (92.7%)	9 (28.1%)	3 (15.0%)	0
0.49-0.74	10 (6.1%)	43 (55.8%)	13 (44.8%)	0	6 (7.3%)	22 (68.8%)	8 (40.0%)	0
0.75-1.00	0	2 (2.6%)	14 (48.3%)	0	0	1 (3.1%)	9 (45.0%)	1
Missing	4	3	2	1	2	3	0	0

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.

Source: Table 9-6 of the Clinical Study Report

Table 9–6 of the Clinical Study Report summarizes shifts in fibrosis stage based on FibroTest score at Week 48 for the FAS. At Week 48, shifts in FibroTest categories relative to baseline categories were similar between the 2 groups.

Table 23: Percentage of Subjects with HBV DNA < 29 IU/mL (Target Not Detected, Target Detected) at Week 48, Missing = Failure (Study GS-US-320-0110)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
HBV DNA at Week 48				
< 29 IU/mL	371/581 (63.9%)	195/292 (66.8%)	0.25	−3.6% (−9.8% to 2.6%)
95% CI	59.8% to 67.8%	61.1% to 72.2%		
< 29 IU/mL Target Not Detected	18/581 (3.1%)	9/292 (3.1%)		
< 29 IU/mL Target Detected	353/581 (60.8%)	186/292 (63.7%)		

Prop Diff = difference in proportions
The denominator for percentages is based on the number of subjects in the Full Analysis Set.
P-value, proportion difference, and 95% CI were based on a dichotomized response: success (HBV DNA < 29 IU/mL) or failure (HBV DNA ≥ 29 IU/mL or missing).
a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-2 of the Clinical Study Report

The proportion of subjects with HBV DNA < 29 IU/mL (target not detected) was numerically the same for TAF and TDF (3.1% in both treatment arms).

Table 24: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48, Missing = Excluded (Study GS-US-320-0110)

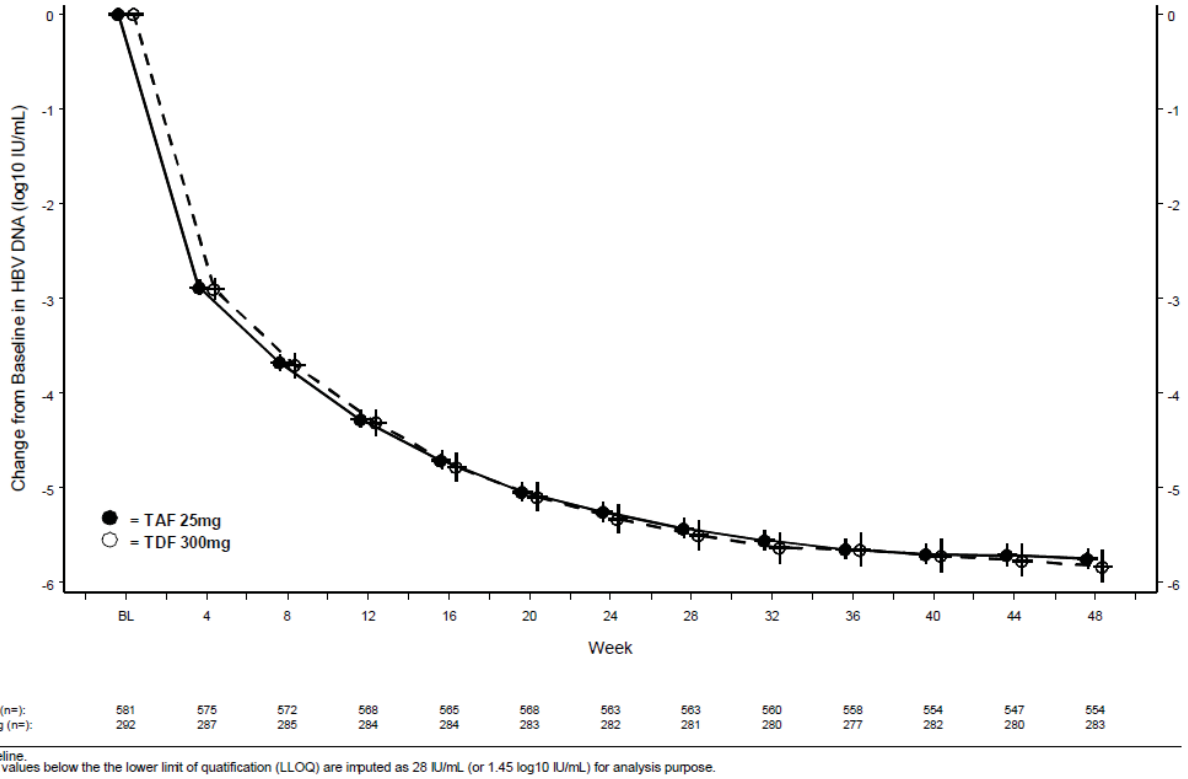
	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
HBV DNA at Week 48				
< 29 IU/mL	371/554 (67.0%)	195/283 (68.9%)	0.37	−2.8% (−9.0% to 3.4%)
95% CI	62.9% to 70.9%	63.2% to 74.3%		
< 29 IU/mL Target Not Detected	18/554 (3.2%)	9/283 (3.2%)		
< 29 IU/mL Target Detected	353/554 (63.7%)	186/283 (65.7%)		

Prop Diff = difference in proportions
The denominator for percentage is the number of subjects in the Full Analysis Set with nonmissing HBV DNA value at each visit.
P-value, proportion difference, and 95% CI were based on a dichotomized response: success (HBV DNA < 29 IU/mL) or failure (HBV DNA ≥ 29 IU/mL or missing).
a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.
b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-3 of the Clinical Study Report

Compared to the primary efficacy analysis that assumed patients who were missing to be failures (M=F) slightly higher response rates were observed for the primary efficacy endpoint in both treatment arms using the missing=excluded imputation (67% for TAF and 69% for TDF) but the difference between both treatment groups didn't change enough to affect the conclusion of NI. The proportion of subjects with HBV DNA < 29 IU/mL (target not detected) was numerically the same for TAF and TDF (3.2% in both treatment arms).

Figure 9: Mean and 95% CIs of Change from Baseline in HBV DNA (log10 IU/mL) by Visit (Observed Data) (Study GS-US-320-0110)



	BL	4	8	12	16	20	24	28	32	36	40	44	48
TAF 25mg (n=):	581	575	572	568	565	568	563	563	560	558	554	547	554
TDF 300mg (n=):	292	287	285	284	284	283	282	281	280	277	282	280	283

BL = Baseline.
HBV DNA values below the the lower limit of quatification (LLOQ) are imputed as 28 IU/mL (or 1.45 log10 IU/mL) for analysis purpose.

Source: Figure 9-2 of the Clinical Study Report

Similar patterns were observed for mean changes from baseline for Study GS-US-320-0110. As can be seen in Figure 9-2 of the Clinical Study Report all of the 95% confidence intervals overlapped. However these results were based on observed data so the effect of missing data was not accounted for.

Table 25: Percentage of Subjects with Normalized ALT at Week 48, Missing = Failure (Study GS-US-320-0110, Full Analysis Set)

	TAF 25 mg	TDF 300 mg	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
Normalized ALT (Central Laboratory)				
Week 48	384/537 (71.5%)	179/268 (66.8%)	0.18	4.6% (−2.3% to 11.4%)
Normalized ALT (AASLD)				
Week 48	257/572 (44.9%)	105/290 (36.2%)	0.014	8.7% (1.8% to 15.6%)

AASLD = American Association for the Study of Liver Disease; Prop Diff = difference in proportions

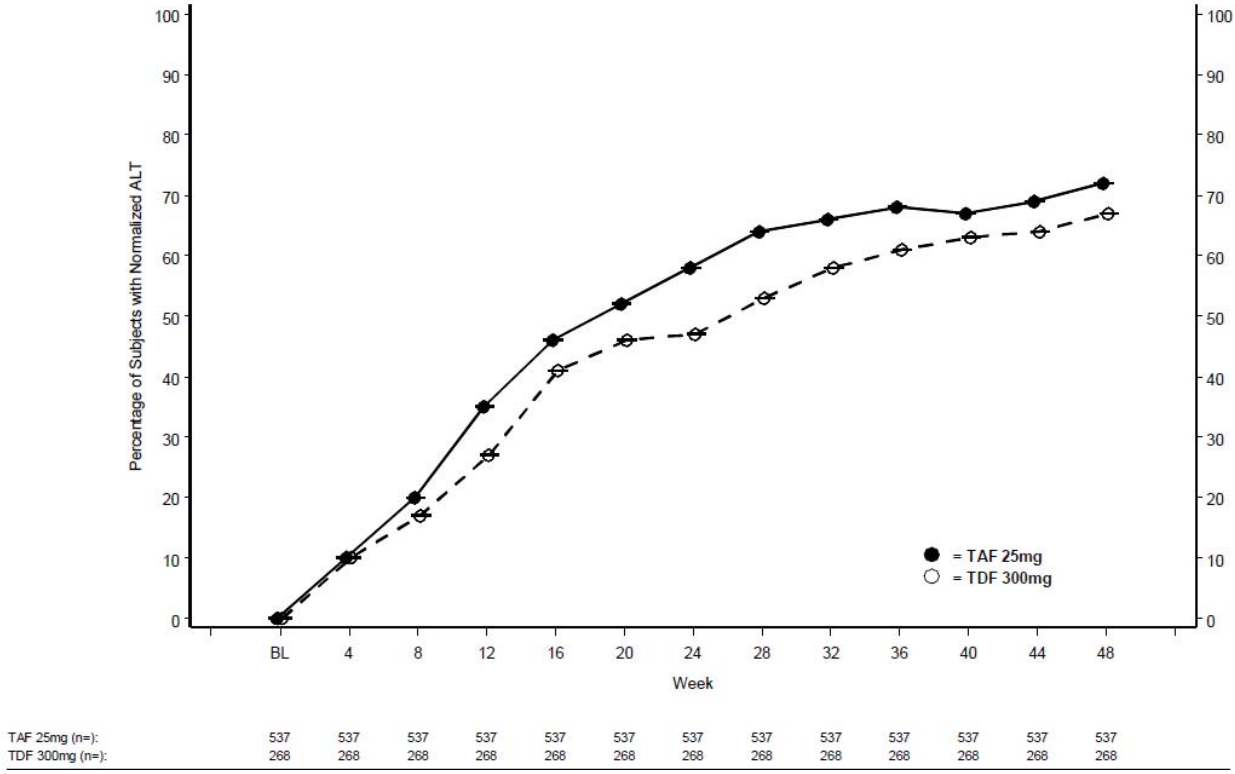
a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.

b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Table 9-4 of the Clinical Study Report

Using the central laboratory criteria, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) was numerically higher for the TAF group (72%) compared to the TDF group (67%) (p=0.18). Using the AASLD criteria (≤30 U/L for men and ≤19 U/L for women), the percentage of subjects with normalized ALT was significantly higher in the TAF group (45%) than in the TDF group (36%) (p=0.014) at Week 48 using the M = F method.

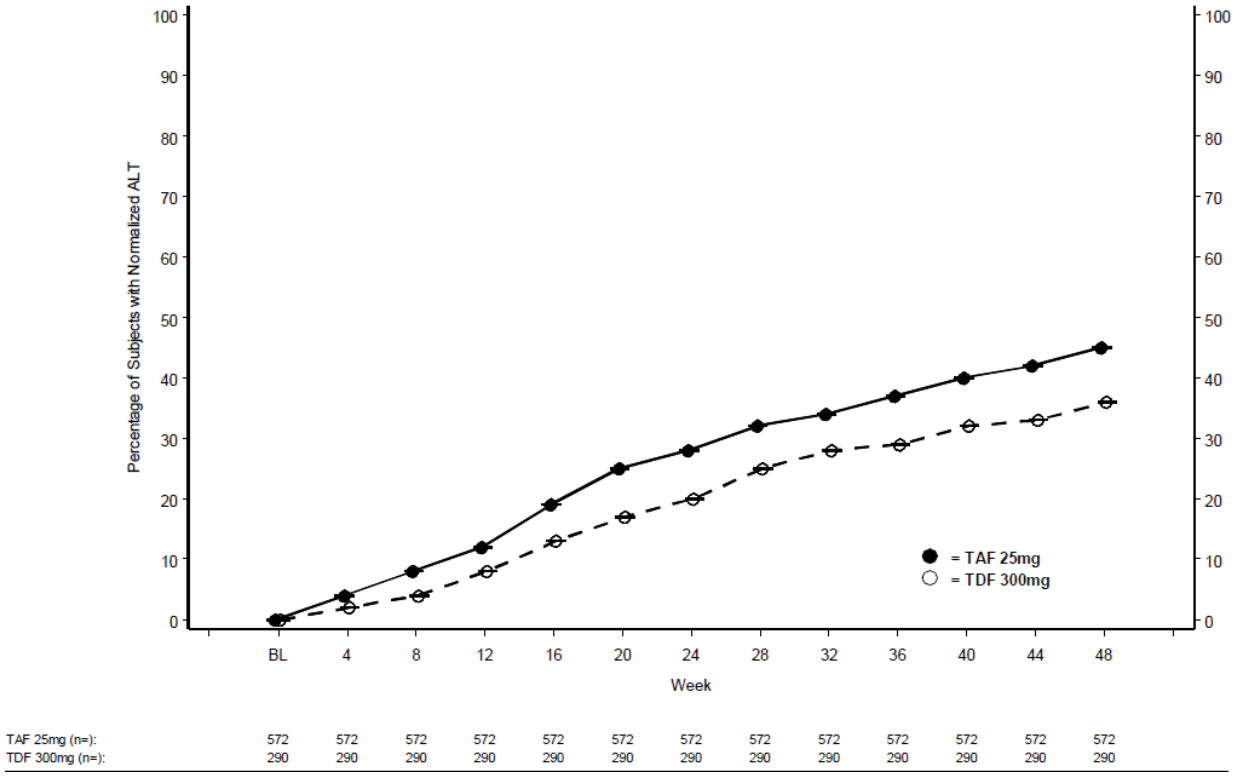
Figure 10: Percentage of Subjects with ALT Normalization by Visit, Missing = Failure (Central Laboratory Criteria) (Study GS-US-320-0110, Full Analysis Set)



Source: Figure 9-3 of the Clinical Study Report

Using the central laboratory criteria, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 8 through 48.

Figure 11: Percentage of Subjects with ALT Normalization by Visit, Missing = Failure (AASLD Criteria) (Study GS-US-320-0110, Full Analysis Set)



Source: Figure 9-4 of the Clinical Study Report

Response rates at each post-baseline visit using AASLD criteria for both treatment arms were lower than they were using Central Laboratory criteria. According to the applicant, the percentage of subjects with normalized ALT using the AASLD criteria was significantly higher in the TAF group than in the TDF group at all time-points from Week 8 onward using the M = F method.

Table 26: Proportion of Subjects with HBeAg Loss/Seroconversion by Visit, Missing = Failure (Study GS-US-320-0110, Serologically Evaluable Full Analysis Set)

	TAF 25 mg	TDF 300 mg	TAF 25 mg vs TDF 300 mg	
			P-Value[a]	Prop Diff (95% CI)[b]
HBeAg Loss				
Week 48	78/565 (13.8%)	34/285 (11.9%)	0.47	1.8% (−3.0% to 6.5%)
HBeAg Seroconversion				
Week 48	58/565 (10.3%)	23/285 (8.1%)	0.32	2.1% (−2.0% to 6.3%)

Prop Diff = difference in proportions

a P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata.

b Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion includes subjects with HBeAg positive and HBeAb negative/missing at baseline.

HBeAg loss was defined as changes from HBeAg positive at baseline to HBeAg negative at a postbaseline with baseline HBeAb negative/missing.

HBeAg seroconversion was defined as HBeAg loss and HBeAb changes from negative/missing at baseline to positive at a postbaseline visit.

Source: Table 9-5 of the Clinical Study Report

Because noninferiority of TAF relative to TDF was established, multiplicity adjustments were performed for the key secondary endpoints. HBeAg loss and seroconversion was the fifth key alpha-controlled endpoint for this study. According to the applicant, because the fourth key alpha-controlled endpoint was not significantly different at Week 48 (proteinuria by urinalysis [dipstick], Section 11.2.4.2.2.3 of the Clinical Study Report), formal statistical testing was not done for HBeAg loss and seroconversion.

A total of 78 (14%) and 34 (12%) subjects in the TAF and TDF groups, respectively, experienced HBeAg loss at Week 48. A total of 58 (10%) and 23 (8%) subjects in the TAF and TDF groups, respectively, experienced HBeAg loss with seroconversion at Week 48. According to the applicant, a total of 4 subjects (0.7%) in the TAF group and 1 subject (0.3%) in the TDF group experienced HBsAg loss at Week 48. Three of the 4 subjects in the TAF group and no subject in the TDF group also experienced HBsAg seroconversion.

Table 27: FibroTest Score and Change from Baseline in FibroTest Score by Visit (Study GS-US-320-0110)

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg	
			P-Value	Diff in LSM (95% CI)
Baseline				
N	566	282	0.31	0.02 (−0.02, 0.05)
Mean (SD)	0.34 (0.227)	0.32 (0.225)		
95% CI	(0.32 , 0.36)	(0.30 , 0.35)		
Median	0.29	0.25		
Q1, Q3	0.16, 0.48	0.14, 0.47		
Min, Max	0.04, 0.98	0.03, 0.99		
At Week 48				
N	552	282		
Mean (SD)	0.27 (0.200)	0.28 (0.218)		
95% CI	(0.25 , 0.29)	(0.26 , 0.31)		
Median	0.21	0.21		
Q1, Q3	0.12, 0.37	0.11, 0.40		
Min, Max	0.00, 0.91	0.00, 0.93		
Change at Week 48				
N	537	274	0.007	−0.03 (−0.04, −0.01)
Mean (SD)	−0.07 (0.127)	−0.04 (0.121)		
95% CI	(−0.08 , −0.06)	(−0.06 , −0.03)		
Median	−0.05	−0.04		
Q1, Q3	−0.12, 0.01	−0.10, 0.02		
Min, Max	−0.69, 0.27	−0.65, 0.46		

Diff = difference; LSM = least-squares mean
P-value, difference in least-squares means, and its 95% CI were from ANOVA model with baseline HBV DNA categories, oral antiviral treatment status, and treatment group as fixed effects in the model.

Source: Table 9-6 of the Clinical Study Report

Table 9–6 of the Clinical Study Report presents the change from baseline in FibroTest scores for the FAS. At Week 48, the mean (SD) change from baseline in FibroTest scores in the TAF group was −0.07 (0.13) and in the TDF group was −0.04 (0.12) (least-squares means [LSM] difference: −0.03, 95% CI: −0.04 to −0.01; p = 0.007).

Table 28: Shift Table of Fibrosis Stage by FibroTest by Visit (Study GS-US-320-0110)

	TAF 25 mg (N = 581) Baseline				TDF 300 mg (N = 292) Baseline			
	0.00–0.48 (N = 432)	0.49–0.74 (N = 89)	0.75–1.00 (N = 45)	Missing (N = 15)	0.00–0.48 (N = 213)	0.49–0.74 (N = 47)	0.75–1.00 (N = 22)	Missing (N = 10)
At Week 48								
0.00–0.48	401 (96.9%)	51 (60.0%)	5 (13.2%)	12	200 (96.6%)	23 (50.0%)	1 (4.8%)	8
0.49–0.74	13 (3.1%)	29 (34.1%)	16 (42.1%)	3	6 (2.9%)	20 (43.5%)	10 (47.6%)	0
0.75–1.00	0	5 (5.9%)	17 (44.7%)	0	1 (0.5%)	3 (6.5%)	10 (47.6%)	0
Missing	18	4	7	0	6	1	1	2

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.

Source: Table 9-7 of the Clinical Study Report

Table 9–7 of the Clinical Study Report summarizes shifts in fibrosis stage based on FibroTest score at Week 48 for the FAS. At Week 48, shifts in FibroTest categories relative to baseline categories were similar between the 2 groups.

3.3 Evaluation of Safety

Table 29: Reviewer's Analysis of Fasting Lipid Parameters at Week 48 (Studies GS-US-320-0108 and GS-US-320-0110, Safety Analysis Set)

Change from Baseline (mg/dL)	Pooled arm TAF N=866	Pooled arm TDF N=432
Fasting Cholesterol (N) Mean Median Q1, Q3 p-value	771 0 -2 (-17,17) <0.001	393 -25 -24 (-42,-6)
Fasting LDL (N) Mean Median Q1, Q3 p-value	771 6 4 (-8,20) <0.001	393 -11 -9 (-24,5)
Fasting HDL (N) Mean Median Q1, Q3 p-value	770 -4 -3 (-10,2) <0.001	393 -10 -9 (-17,-3)
Triglycerides (N) Mean Median Q1, Q3 p-value	772 11 6 (-13,26) <0.001	393 -10 -7 (-27,10)
Cholesterol (N) Mean Median Q1, Q3 p-value	829 0 -2 (-17,16) <0.001	417 -24 -23 (-41,-6)

Source: Reviewer's Analysis

In a combined analysis of the two pooled phase 3 trials, subjects in the TDF group showed decreases from baseline in fasting cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and cholesterol that were significantly different in comparison to the TDF group ($p < 0.001$). The applicant's results were similar to those obtained by the reviewer. The median change from baseline in the fasting total cholesterol to HDL ratio was 0.2 for the TAF and TDF groups ($p = 0.016$). For detailed safety evaluation, please refer to the clinical review written by Dr. Tanvir Bell.

Table 30: Applicant's Measures of Fasting Lipid Parameters at Week 48 (Studies GS-US-320-0108 and GS-US-320-0110, Safety Analysis Set)

	Median Change From Baseline (Q1, Q3)				
Fasting Metabolic Assessment[a]	**N**	**TAF 25 mg (N = 866)**	**N**	**TDF 300 mg (N = 432)**	**P-Value[b]**
Total Cholesterol (mg/dL)	772	−2 (−17, 17)	394	−24 (−42, −6)	< 0.001
Direct LDL Cholesterol (mg/dL)	772	4 (−9, 20)	394	−9 (−25, 5)	< 0.001
HDL Cholesterol (mg/dL)	771	−3 (−10, 2)	394	−9 (−17, −3)	< 0.001
Total Cholesterol to HDL Ratio	771	0.2 (−0.1, 0.5)	394	0.2 (−0.2, 0.5)	0.16
Triglycerides (mg/dL)	773	6 (−13, 26)	394	−7 (−27, 10)	< 0.001

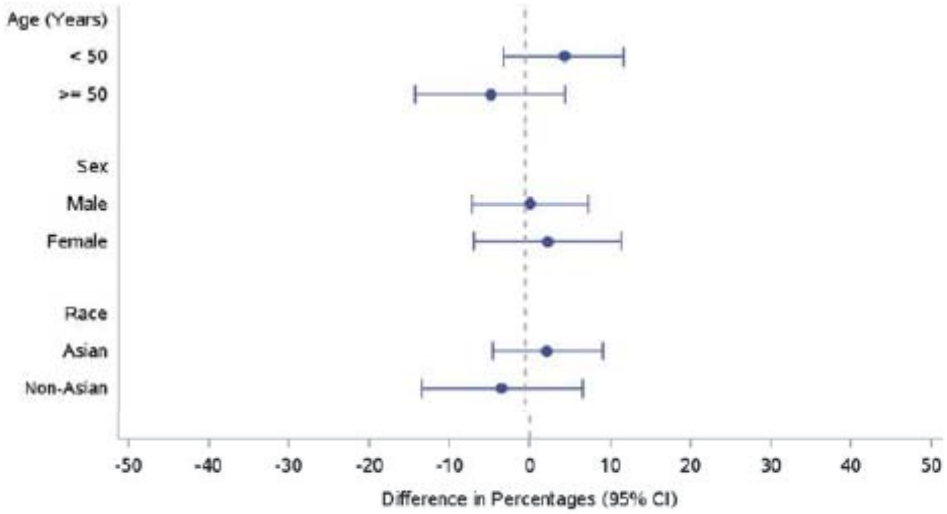
a Only laboratory measurements under fasting status were summarized.
b P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Source: Table 10 in the Clinical Overview

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and other factors

Figure 12: Forest Plot of Risk Differences for Subjects with HBV DNA < 29 IU/mL at Week 48 by Baseline Age, Sex and Race Subgroups (Study GS-US-320-0108)



Source: Figure 9-5 in the Clinical Study Report

For both trials at Week 48, the rates of HBV DNA <29 IU/mL for subgroups according to age (<50 years vs ≥50 years), sex, and race (Asian vs non-Asian) did not differ statistically for the TAF group compared with the TDF group. None of the applicant's homogeneity tests of treatment interaction with age, gender and race were statistically significant (see Appendix for details) and 95% CIs for risk-differences overlapped.

Table 31: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 by Age, Sex and Race Subgroups, Missing = Failure (Study GS-US-320-0108)

	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg Prop Diff (95% CI)[a]
Age (years)			
< 50	171/176 (97.2%)	64/69 (92.8%)	4.9% (−2.7% to 12.4%)
≥ 50	97/109 (89.0%)	66/71 (93.0%)	−4.4% (−13.9% to 5.0%)
Sex			
Male	162/173 (93.6%)	80/86 (93.0%)	0.6% (−6.7% to 7.9%)
Female	106/112 (94.6%)	50/54 (92.6%)	2.8% (−6.5% to 12.0%)
Race			
Asian	192/205 (93.7%)	92/101 (91.1%)	2.7% (−4.2% to 9.7%)
Non-Asian	76/80 (95.0%)	38/39 (97.4%)	−3.0% (−13.1% to 7.2%)

Source: Table 9-7 in the Clinical Study Report

Figure 13: Forest Plot of Risk Differences for Subjects with HBV DNA < 29 IU/mL at Week 48 by Age, Sex and Race Subgroups, Missing = Failure (Study GS-US-320-0110)

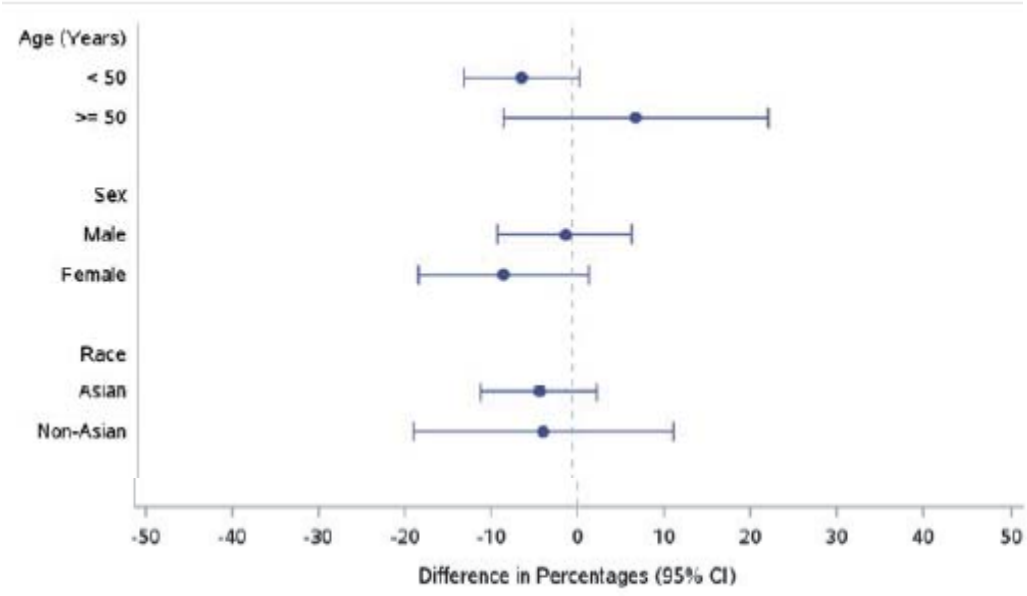


Table 32: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 by Age, Sex and Race Subgroups, Missing = Failure (Study GS-US-320-0110)
Study GS-US-320-0110

	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg
			Prop Diff (95% CI)[a]
Age (Years)			
< 50	313/493 (63.5%)	161/234 (68.8%)	−6.0% (−12.8% to 0.8%)
≥ 50	58/88 (65.9%)	34/58 (58.6%)	7.5% (−8.1% to 23.1%)
Sex			
Male	228/371 (61.5%)	120/189 (63.5%)	−0.9% (−8.9% to 7.0%)
Female	143/210 (68.1%)	75/103 (72.8%)	−8.2% (−18.3% to 2.0%)
Race			
Asian	321/482 (66.6%)	162/232 (69.8%)	−3.9% (−10.8% to 2.9%)
Non-Asian	50/99 (50.5%)	33/60 (55.0%)	−3.5% (−18.8% to 11.9%)

Source: Table 9-8 in the Clinical Study Report

Table 33: Percentage of subjects with Normalized ALT at Week 48 by Sex using the AASLD definition (Study GS-US-320-0108)

	TAF 25mg (Total=276)	TDF 300mg (Total=138)	TAF - TDF
Sex	**n/N (%)**	**n/N (%)**	
Female	43/111 (39%)	13/53 (25%)	14% (-2% to +28%)
Male	94/165 (57%)	31/85 (36%)	21% (7% to 33%)

p-value from Zelen's test= 0.82
Source: Reviewer's Analysis

Table 34: Percentage of subjects with Normalized ALT at Week 48 by Sex using the AASLD definition (Study GS-US-320-0110)

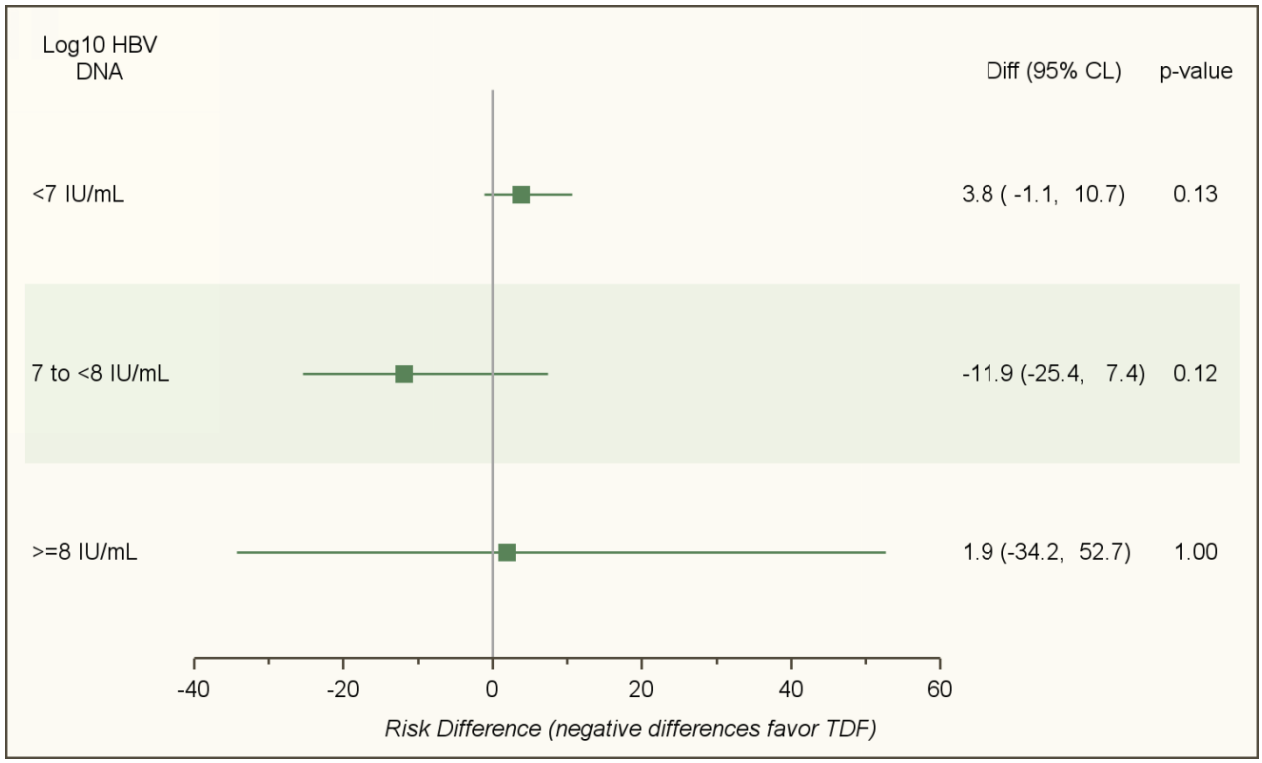
	TAF 25mg (Total=572)	TDF 300mg (Total=290)	TAF - TDF
Sex	**n/N (%)**	**n/N (%)**	
Female	86/208 (41%)	34/103 (33%)	8% (-3% to +19%)
Male	171/364 (47%)	71/187 (38%)	9% (0.002% to 18%)

p-value from Zelen's test= 1.00
Source: Reviewer's Analysis

The AASLD criteria for normalized ALT were ≤30 U/L for men and ≤19 U/L for women. Since the AASLD definition differed for men and women separate analyses by gender were performed. Treatment differences were larger for males, particularly in GS-US-320-0108 and were statistically significant in both trials for males. Although not statistically significant in females, the treatment difference was in the same direction, which is why the Zelen test for interaction was not statistically significant for either trial.

Other Special/Subgroup Populations

Figure 14: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using the three baseline HBV DNA randomization strata (Study GS-US-320-0108)



Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test= 0.13

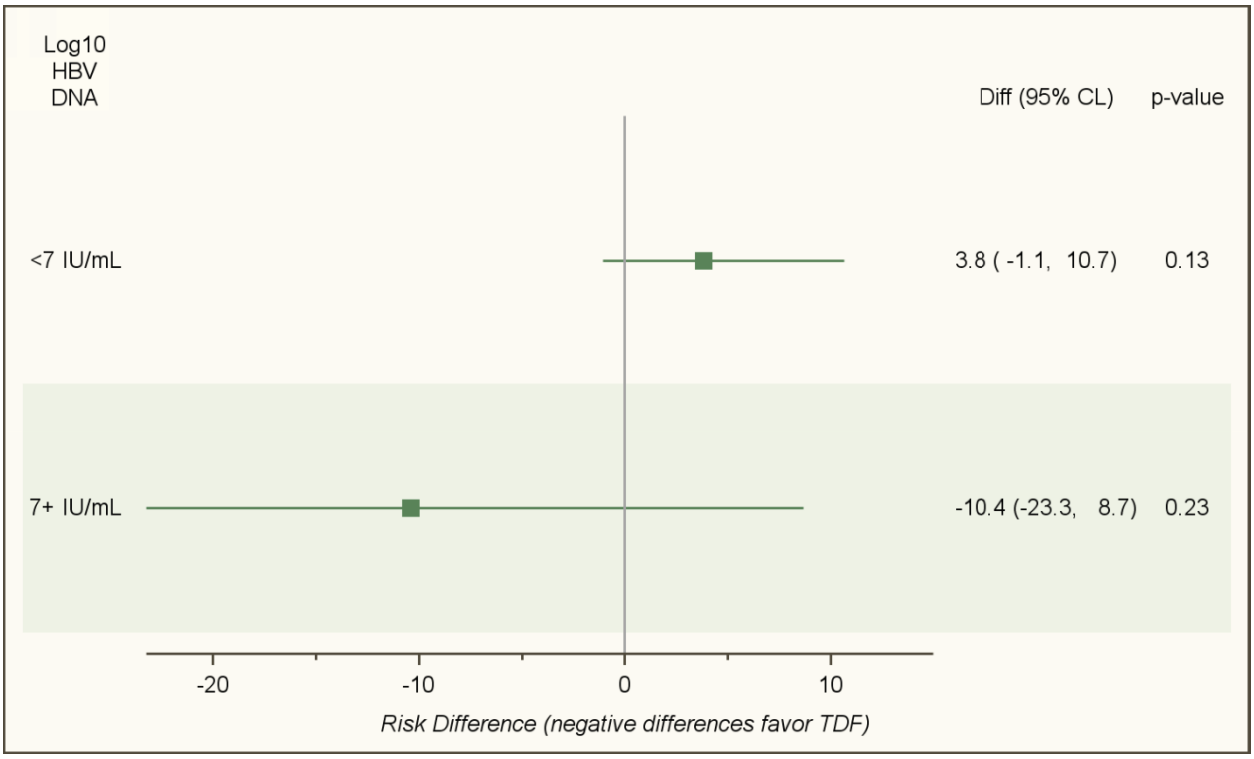
The applicant stratified the randomization by the three baseline HBV DNA strata shown above. Given there were only 13 subjects randomized to TAF and only 4 subjects randomized to TDF with baseline HBV DNA that was at least 8 $\log_{10}$ IU/mL the 95% CI's were extremely wide. Therefore the subjects in the last two subgroups should be combined into a single stratum (≥7 $\log_{10}$ IU/mL).

Table 35: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using the three baseline HBV DNA randomization strata (Study GS-US-320-0108)

log10 HBV DNA	TAF 25mg (Total=285)		TDF 300mg (Total=140)	
	N	n (%)	N	n (%)
<7 IU/mL	230	221 (96.1)	116	107 (92.2)
7 to <8 IU/mL	42	37 (88.1)	20	20 (100.0)
>=8 IU/mL	13	10 (76.9)	4	3 (75.0)

Source: Statistical Analyst's table with input from the Reviewer

Figure 15: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL, Study GS-US-320-0108)



Source: Statistical Analyst's graph with input from the Reviewer

p-value for Zelen's test=0.086

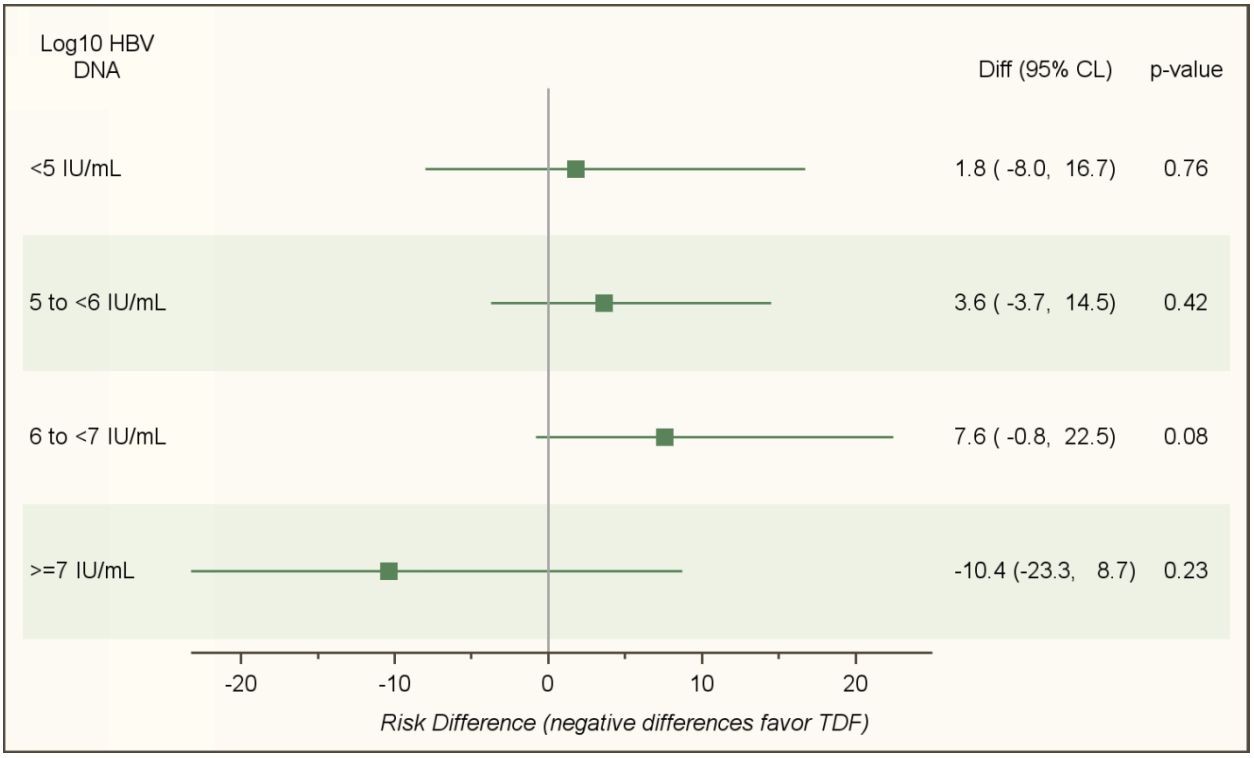
For subjects with baseline HBV DNA ≥ 7 log10 IU/mL, a numerically higher proportion achieved HBV DNA < 29 IU/mL at Week 48 in the TDF group compared with the TAF group. Zelen's homogeneity test of treatment effect by baseline HBV DNA was not quite statistically significant at the 0.05 level (p=0.086). Forest plots using other dichotomous cut-points are shown in the Appendix.

Table 36: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL, Study GS-US-320-0108)

log_{10} HBV DNA	TAF 25mg (Total=285)		TDF 300mg (Total=140)	
	N	n (%)	N	n (%)
<7 IU/mL	230	221 (96.1)	116	107 (92.2)
7+ IU/mL	55	47 (85.5)	24	23 (95.8)

Source: Statistical Analyst's table with input from the Reviewer

Figure 16: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using four baseline HBV DNA subgroups (Study GS-US-320-0108)



Source: Statistical Analyst's graph with input from the Reviewer

p-value for Zelen's test=0.15

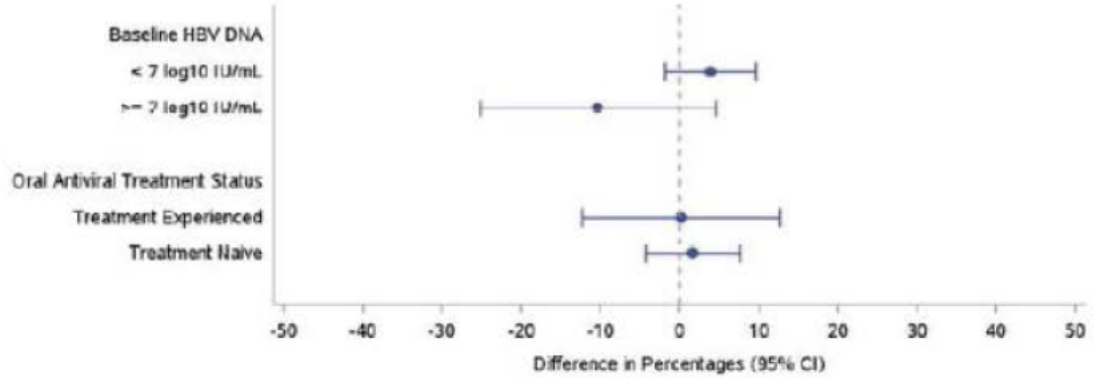
In order to verify that the shift in response occurred at 7 $\log_{10}$ IU/mL and not at lower values, the reviewer looked at four approximately equal strata using 1 $\log_{10}$ IU/mL increments. Although there was some variability for subgroups with baseline HBV DNA<7 $\log_{10}$ IU/mL, each of the point estimates favored TAF over TDF. The reverse trend appears to have been true for high baseline viral loads exceeding 7 $\log_{10}$ IU/mL, although the interaction was not statistically significant.

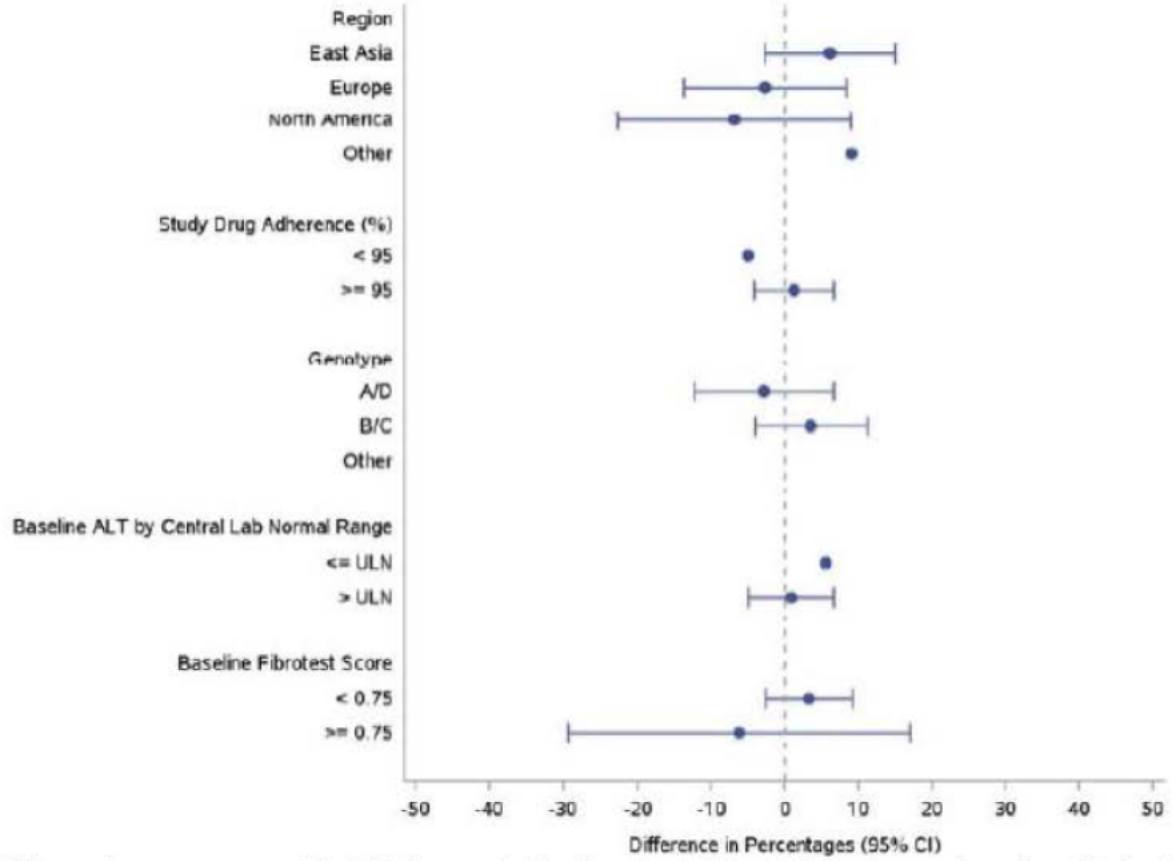
Table 37: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using four baseline HBV DNA subgroups for Study GS-US-320-0108

log_{10} HBV DNA	TAF 25mg (Total=285)		TDF 300mg (Total=140)	
	N	n (%)	N	n (%)
<5 IU/mL	85	79 (92.9)	34	31 (91.2)
5 to <6 IU/mL	80	78 (97.5)	49	46 (93.9)
6 to <7 IU/mL	65	64 (98.5)	33	30 (90.9)
>=7 IU/mL	55	47 (85.5)	24	23 (95.8)

Source: Statistical Analyst's table with input from the Reviewer

Figure 17: Forest Plots of Risk Differences for Subjects with HBV DNA < 29 IU/mL at Week 48 by Other Baseline Characteristics (Study GS-US-320-0108)





Difference in response rates and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata (if not the subgroup factor).
The 95% CIs of the difference in response rates were not provided for some subgroups since they were not calculable.
For this subgroup analysis, 2-level baseline HBV DNA categories (< 7 $\log_{10}$ IU/mL and ≥ 7 $\log_{10}$ IU/mL) were used.
Relative to the vertical line at 0, differences on the right favor the TAF group and differences on the left favor the TDF group.

Source: Figure 9-5 of the Clinical Study Report

The applicant provided corresponding forest plots for selected subgroups. None of the interactions appeared to be as large as those observed for baseline viral load and none of the applicant's homogeneity tests performed showed any statistically significant treatment group differences in response rates across any of the baseline strata (see Appendix for details).

Table 38: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 by Other Baseline Subgroups, Missing = Failure (Study GS-US-320-0108)

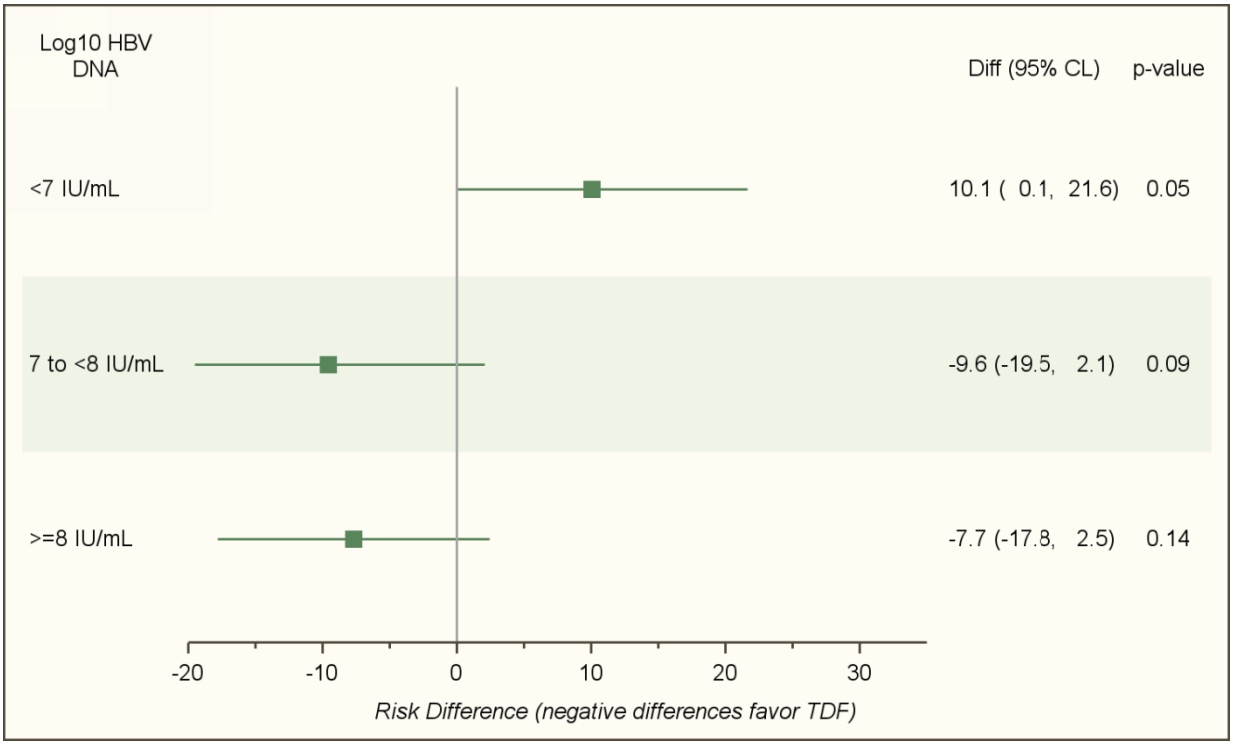
	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg vs TDF 300 mg Prop Diff (95% CI)[a]
Baseline HBV DNA[b]			
< 7 $\log_{10}$ IU/mL	221/230 (96.1%)	107/116 (92.2%)	3.8% (−1.9% to 9.6%)
≥ 7 $\log_{10}$ IU/mL	47/55 (85.5%)	23/24 (95.8%)	−10.4% (−25.2% to 4.5%)
Oral Antiviral Treatment Status			
Treatment Experienced	56/60 (93.3%)	28/30 (93.3%)	0.2% (−12.4% to 12.7%)
Treatment Naive	212/225 (94.2%)	102/110 (92.7%)	1.6% (−4.3% to 7.6%)
Region			
East Asia	110/114 (96.5%)	58/64 (90.6%)	6.1% (−2.8% to 15.0%)
Europe	69/73 (94.5%)	35/36 (97.2%)	−2.7% (−13.8% to 8.4%)
North America	46/53 (86.8%)	28/30 (93.3%)	−6.9% (−22.8% to 8.9%)
Other	43/45 (95.6%)	9/10 (90.0%)	9.0% (NC)
Study Drug Adherence (%)[c]			
< 95	3/4 (75.0%)	5/6 (83.3%)	−5.0% (NC)
≥ 95	265/281 (94.3%)	125/134 (93.3%)	1.2% (−4.2% to 6.6%)
Genotype			
A/D	98/105 (93.3%)	46/48 (95.8%)	−2.9% (−12.3% to 6.6%)
B/C	165/175 (94.3%)	79/87 (90.8%)	3.5% (−4.1% to 11.2%)
Other	5/5 (100.0%)	5/5 (100.0%)	NC (NC)
Baseline ALT by Central Lab Normal Range			
≤ ULN	46/49 (93.9%)	17/19 (89.5%)	5.5% (NC)
> ULN	222/236 (94.1%)	113/121 (93.4%)	0.8% (−5.0% to 6.6%)
Baseline FibroTest Score			
< 0.75	237/249 (95.2%)	110/119 (92.4%)	3.2% (−2.6% to 9.1%)
≥ 0.75	27/31 (87.1%)	19/20 (95.0%)	−6.2% (−29.3% to 17.0%)

NC = not calculable; Prop Diff = difference in proportions
The Week 48 window was between Days 322 and 363 (inclusive).

a Difference in response rates and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata (if not the subgroup factor).
b For this subgroup analysis, 2-level baseline HBV DNA categories (< 7 $\log_{10}$ IU/mL and ≥ 7 $\log_{10}$ IU/mL) were used.
c Study drug adherence subgroups analysis was based on the adherence up to Week 48 visit for active study drug.

Source: Table 9-7 of the Clinical Study Report

Figure 18: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) by using three baseline HBV DNA subgroups (Study GS-US-320-0110)



Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test= 0.02

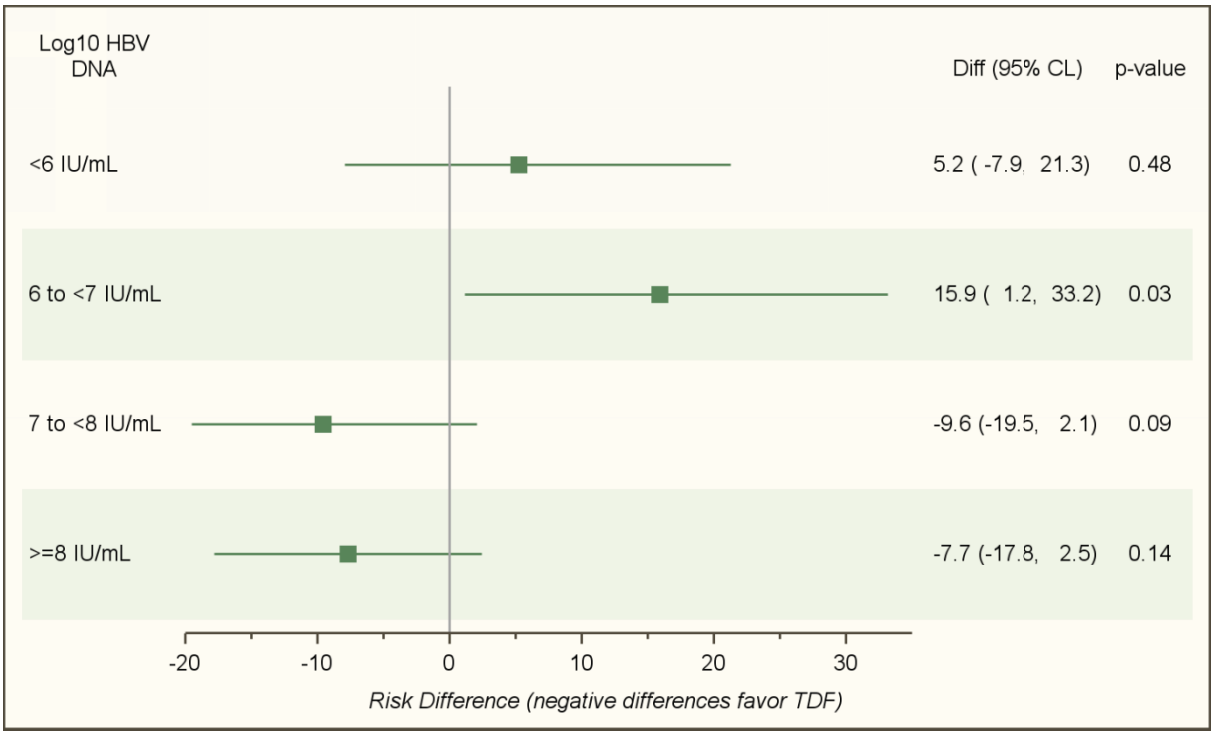
The applicant stratified the second phase 3 trial by only two baseline HBV DNA strata using 8 $\log_{10}$ IU/mL as a cutoff. When the reviewer used the same baseline HBV DNA strata that were used for Study GS-US-320-0108 the Zelen exact test for treatment by baseline interaction was statistically significant (p=0.02) due to the lack of homogeneity of treatment effect in the three baseline HBV DNA strata. While TAF appeared to be superior to TDF for subjects with low baseline viral loads (p=0.049), subjects in the two strata with baseline HBV DNA of at least 7 $\log_{10}$ IU/mL had much higher observed response rates on TDF than on TAF. The applicant's analysis that used the baseline strata (<8 vs. ≥8 $\log_{10}$ IU/mL) did not show as much of a difference because it combined the two strata below 8 $\log_{10}$ IU/mL.

Table 39: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 using three baseline HBV DNA subgroups (Study GS-US-320-0110)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<7 IU/mL	150	132 (88.0)	77	60 (77.9)
7 to <8 IU/mL	159	122 (76.7)	73	63 (86.3)
>=8 IU/mL	272	117 (43.0)	142	72 (50.7)

Source: Statistical Analyst's table with input from the Reviewer

Figure 19: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using four baseline HBV DNA subgroups (Study GS-US-320-0110)



Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=0.027

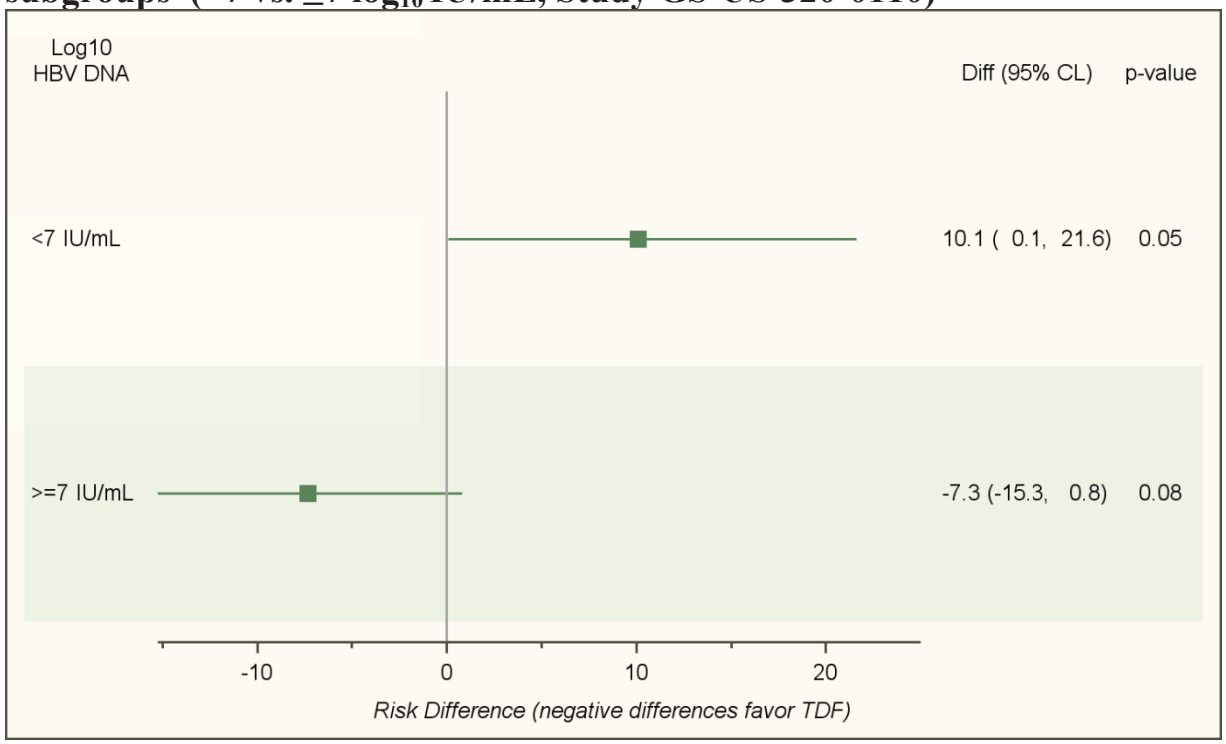
The Zelen exact test for treatment by baseline interaction was also statistically significant (p=0.02) using four baseline HBV DNA strata. TAF had higher observed response rates for the two lowest baseline HBV DNA strata and lower observed response rates for the two baseline strata above 7 $\log_{10}$ IU/mL. Since this trial consisted of HBeAg-Positive subjects, baseline viral loads tended to be higher in this trial than they were for HBeAg-Negative subjects. As a result the four baseline strata in HBeAg-Positive subjects were 1 $\log_{10}$ IU/mL higher than in Study GS-US-320-0108; however the same tipping point was observed in both trials (i.e. the trend reversed when baseline HBV DNA was $\geq$7 $\log_{10}$ IU/mL).

Table 40: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using four baseline HBV DNA subgroups (Study GS-US-320-0110)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<6 IU/mL	84	72 (85.7)	41	33 (80.5)
6 to <7 IU/mL	66	60 (90.9)	36	27 (75.0)
7 to <8 IU/mL	159	122 (76.7)	73	63 (86.3)
>=8 IU/mL	272	117 (43.0)	142	72 (50.7)

Source: Statistical Analyst's table with input from the Reviewer

Figure 20: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL, Study GS-US-320-0110)



Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=0.017

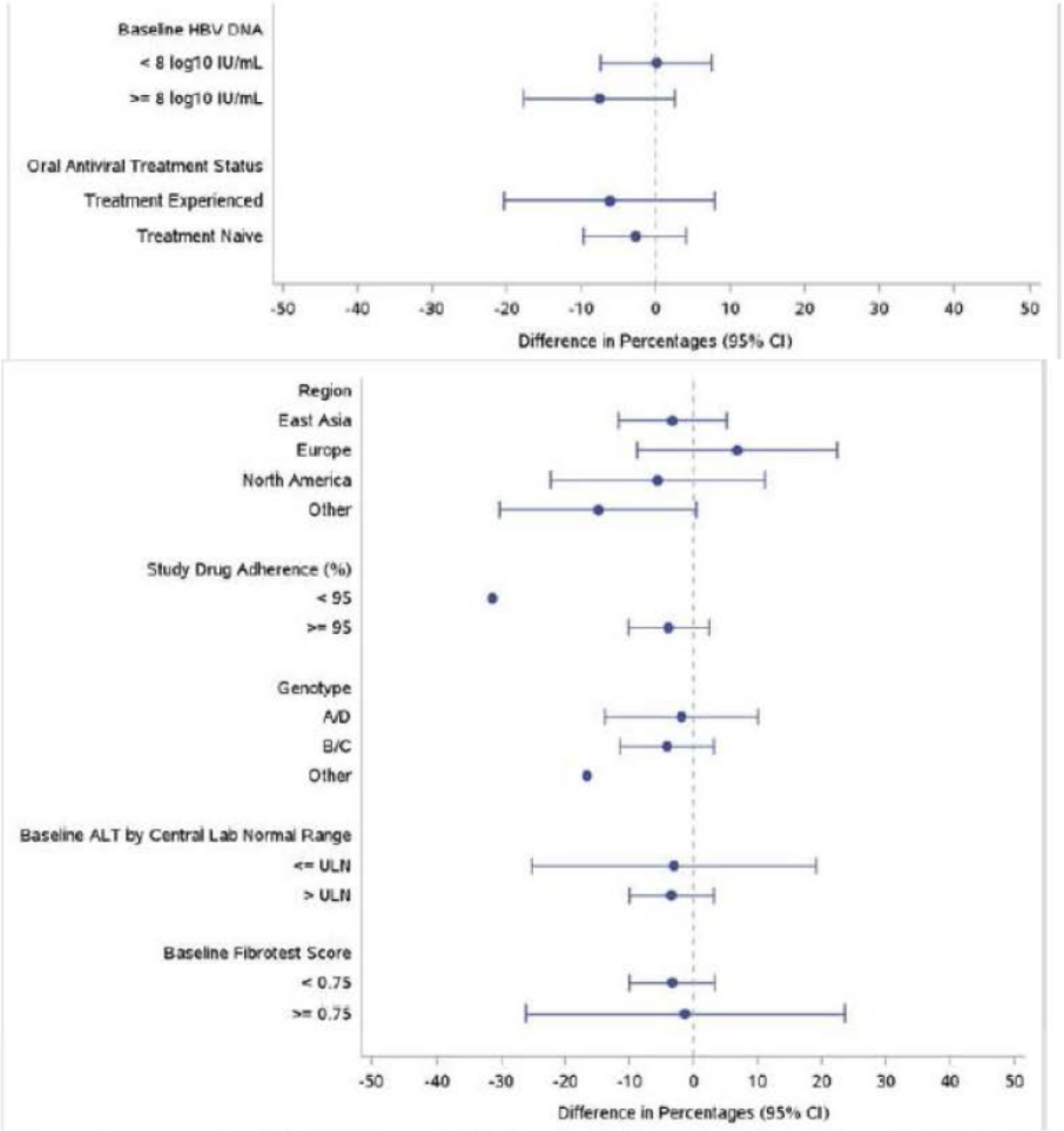
When the cutoff of 7 log_{10} IU/mL was used for Study GS-US-320-0110 the Zelen test was still statistically significant (p=0.017) at the 0.05 level. For subjects with baseline HBV DNA<7 log_{10} IU/mL the difference between TAF and TDF was statistically significant at the 0.05 level (p=0.049, although it was unadjusted for multiple comparisons). Forest plots using other dichotomous cut-points are shown in the Appendix.

Table 41: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL, Study GS-US-320-0110)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<7 IU/mL	150	132 (88.0)	77	60 (77.9)
>=7 IU/mL	431	239 (55.5)	215	135 (62.8)

Source: Statistical Analyst's table with input from the Reviewer

Figure 21: Forest Plots of Risk Differences for Subjects with HBV DNA < 29 IU/mL at Week 48 by Other Baseline Characteristics (Study GS-US-320-0110)



Difference in response rates and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata (if not the subgroup factor).
The 95% CIs of the difference in response rates were not provided for some subgroups since they were not calculable.
Relative to the vertical line at 0, differences on the right favor the TAF group and differences on the left favor the TDF group.

Source: Figure 9-5 of the Clinical Study Report

The applicant provided corresponding forest plots for selected subgroups. None of the interactions appeared to be as large as those observed for baseline viral load. None of the

applicant's homogeneity tests performed showed any statistically significant treatment group differences in response rates across any of the baseline strata (see Appendix for details). Unlike the reviewer's analysis, the applicant's analysis of baseline HBV DNA failed to differentiate between response rates for baseline viral loads between 7 and <8 $\log_{10}$ IU/mL which favored TDF and those below 7 $\log_{10}$ IU/mL which favored TAF. When Gilead combined the strata below 8 $\log_{10}$ IU/mL these appeared to be no difference in response rates between the two treatment arms in the <8 $\log_{10}$ IU/mL subgroup and it was not possible to observe the tipping point which occurred when viral loads exceeded 7 $\log_{10}$ IU/mL.

Table 42: Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 by Other Baseline Subgroups, Missing = Failure (Study GS-US-320-0110)

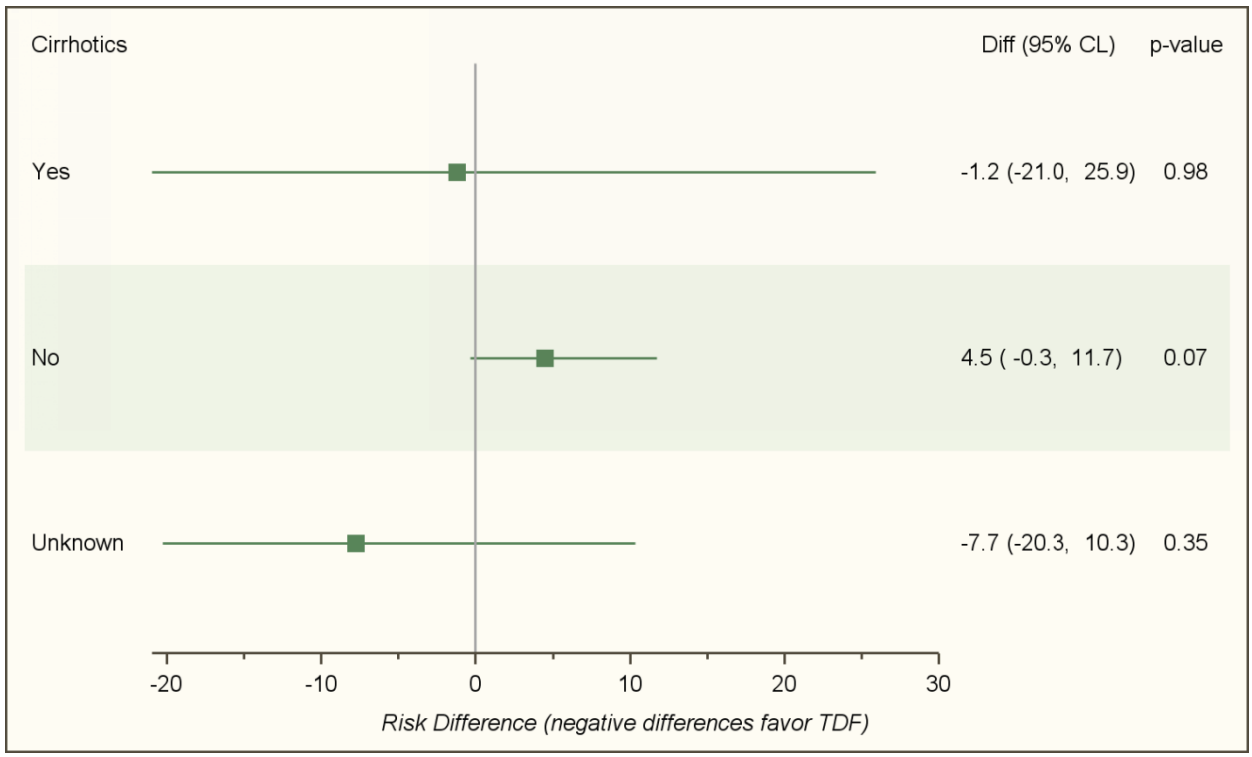
	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)	TAF 25 mg vs TDF 300 mg
			Prop Diff (95% CI)[a]
Baseline HBV DNA			
< 8 $\log_{10}$ IU/mL	254/309 (82.2%)	123/150 (82.0%)	0.1% (−7.4% to 7.5%)
≥ 8 $\log_{10}$ IU/mL	117/272 (43.0%)	72/142 (50.7%)	−7.6% (−17.8% to 2.5%)
Oral Antiviral Treatment Status			
Treatment Experienced	69/137 (50.4%)	39/69 (56.5%)	−6.2% (−20.4% to 7.9%)
Treatment Naive	302/444 (68.0%)	156/223 (70.0%)	−2.8% (−9.7% to 4.1%)
Region			
East Asia	208/287 (72.5%)	110/145 (75.9%)	−3.4% (−11.8% to 5.1%)
Europe	54/104 (51.9%)	24/53 (45.3%)	6.7% (−8.9% to 22.3%)
North America	51/88 (58.0%)	30/49 (61.2%)	−5.7% (−22.3% to 11.0%)
Other	58/102 (56.9%)	31/45 (68.9%)	−14.9% (−30.3% to 0.4%)
Study Drug Adherence (%)[b]			
< 95	10/16 (62.5%)	6/9 (66.7%)	−31.4%[c] (NC)
≥ 95	361/565 (63.9%)	189/280 (67.5%)	−3.9% (−10.2% to 2.4%)
Genotype			
A/D	87/173 (50.3%)	46/88 (52.3%)	−1.9% (−13.8% to 10.0%)
B/C	281/403 (69.7%)	147/200 (73.5%)	−4.3% (−11.6% to 3.0%)
Other	3/5 (60.0%)	2/4 (50.0%)	−16.7%[c] (NC)
Baseline ALT by Central Lab Normal Range			
≤ ULN	26/44 (59.1%)	17/24 (70.8%)	−3.2% (−25.4% to 19.0%)
> ULN	345/537 (64.2%)	178/268 (66.4%)	−3.5% (−10.0% to 3.1%)
Baseline FibroTest Score			
< 0.75	332/521 (63.7%)	172/260 (66.2%)	−3.4% (−10.0% to 3.2%)
≥ 0.75	31/45 (68.9%)	17/22 (77.3%)	−1.4% (−26.2% to 23.5%)

NC = not calculable; Prop Diff = difference in proportions
Week 48 window was between Day 322 and 363 (inclusive).

a Difference in response rates and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata (if not the subgroup factor).
b Study drug adherence subgroups analysis are based on the adherence up to Week 48 visit for active study drug.
c Due to small sample sizes, the point estimate is not reliably calculated.

Source: Table 9-8 of the Clinical Study Report

Figure 22: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) by History of Cirrhosis (Study GS-US-320-0108)



p-value from Zelen's test=0.18
Source: Statistical Analyst's graph with input from the Reviewer

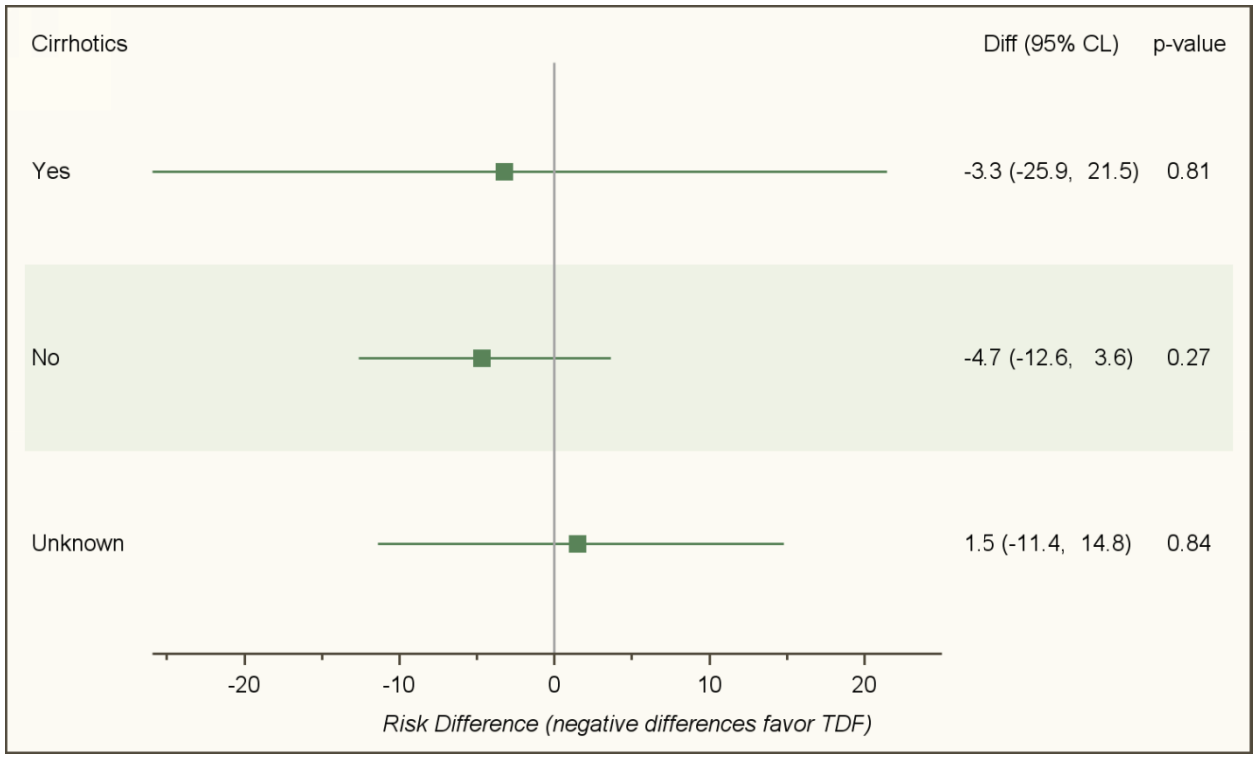
Table 43: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 by History of Cirrhosis (Study GS-US-320-0108)

	TAF 25mg (Total=258)		TDF 300mg (Total=140)	
Cirrhosis	**N**	**n (%)**	**N**	**n (%)**
Yes	24	22 (91.7)	14	13 (92.9)
No	195	190 (97.4)	99	92 (92.9)
Unknown	66	56 (84.8)	27	25 (92.6)

Source: Statistical Analyst's table with input from the Reviewer

In addition the reviewer summarized the primary efficacy analysis by history of cirrhosis and found no interactions between treatment group and history of cirrhosis in either study.

Figure 23: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) by History of Cirrhosis (Study GS-US-320-0110)



p-value from Zelen's test=0.72
Source: Statistical Analyst's graph with input from the Reviewer

Table 44: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 by History of Cirrhosis (Study GS-US-320-0110)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
Cirrhosis	**N**	**n (%)**	**N**	**n (%)**
Yes	41	26 (63.4)	24	16 (66.7)
No	376	245 (65.2)	189	132 (69.8)
Unknown	164	100 (61.0)	79	47 (59.5)

Source: Statistical Analyst's table with input from the Reviewer

Table 45: Percentage of subjects with Normalized ALT at Week 48 by baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL) using the AASLD definition (Study GS-US-320-0108)

log_{10} HBV DNA	TAF 25mg (Total=276)	TDF 300mg (Total=138)	TAF - TDF
	n/N (%)	n/N (%)	
<7 IU/mL	105/221 (48%)	38/114 (33%)	14% (+3% to +25%)
>=7 IU/mL	32/55 (58%)	6/24 (25%)	33% (+9% to +53%)

p-value from Zelen's test= 0.26
Source: Reviewer's Analysis

When the cutoff of 7 log_{10} IU/mL was used for study GS-US-320-0108 the Zelen test was not statistically significant (p=0.26) at the 0.05 level indicating similar trends for patients with low and high baseline viral loads. For subjects with baseline HBV DNA<7 log_{10} IU/mL the difference between TAF and TDF was 14% while there was a difference of 33% in favor of TAF for subjects with baseline viral loads ≥7 log_{10} IU/mL.

Table 46: Percentage of subjects with Normalized ALT at Week 48 by baseline HBV DNA subgroups (<7 vs. ≥7 log_{10} IU/mL) using the AASLD definition (Study GS-US-320-0110)

log_{10} HBV DNA	TAF 25mg (Total=276)	TDF 300mg (Total=138)	TAF - TDF
	n/N (%)	n/N (%)	
<7 IU/mL	69/143 (48%)	17/75 (23%)	26% (+12% to +38%)
>=7 IU/mL	188/429 (44%)	88/215 (41%)	3% (-5% to +11%)

p-value from Zelen's test= 0.006
Source: Reviewer's Analysis

When the cutoff of 7 log_{10} IU/mL was used for study GS-US-320-0110 the Zelen test was statistically significant (p=0.006) at the 0.05 level. For subjects with baseline HBV DNA<7 log_{10} IU/mL the difference between TAF and TDF was 26% while there was no statistically significant difference between the two treatment groups for subjects with baseline viral loads ≥7 log_{10} IU/mL.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The Zelen exact test for treatment by baseline viral load interaction was statistically significant in the HBeAg-Positive trial and close to statistically significant in the HBeAg-Negative trial. Compared to TDF, TAF had higher observed response rates for the subjects with baseline HBV DNA <7 $\log_{10}$ IU/mL and lower observed response rates in subjects with baseline HBV DNA above 7 $\log_{10}$ IU/mL. Since this trial consisted of HBeAg-Positive subjects, baseline viral loads tended to be higher in this trial than they were for HBeAg-Negative subjects. As a result the four baseline strata in HBeAg-Positive subjects were 1 $\log_{10}$ IU/mL higher than in Study GS-US-320-0108; however the same tipping point was observed in both trials (i.e. the trend reversed when baseline HBV DNA was ≥7 $\log_{10}$ IU/mL).

The finding that patients with lower baseline viral loads (<7 IU/mL) had higher response rates in the TAF arm compared to the TDF arm and the reverse trend was observed for subjects with higher baseline viral loads was replicated in both trials. The treatment by baseline HBV DNA viral load interaction was statistically significant in Study GS-US-320-0110 and the same trend was observed in Study GS-US-320-0108. Note that although the applicant pre-specified that they would use just two baseline HBV DNA strata for randomization in Study GS-US-320-0110 (<8 and ≥8 $\log_{10}$ IU/mL) they used three baseline HBV DNA randomization for Study GS-US-320-0108 (<7, 7-<8, ≥8 $\log_{10}$ IU/mL). There is no rationale for the lack of consistent randomization strata across trials. The reviewer would have recommended that the applicant to have used the same strata for both trials or to have used the same number of strata,

The applicant also concluded that higher rates of ALT normalization were seen with TAF than with TDF and that the differences were statistically significant when evaluated by the AASLD criteria. The applicant's pre-specified order of hypothesis testing did not include this secondary efficacy variable so there was no control of the type I error rate for multiple endpoints. However there is less concern about pre-specification of type I error since the statistically significant finding was observed in both trials. The same trend was observed using central laboratory normal ranges but there was no statistically significant difference between TAF and TDF in either trial. In addition the Zelen exact test for treatment by baseline HBV DNA interaction for ALT normalization (using the AASLD criteria) was statistically significant in the HBeAg-Positive trial but was not statistically significant in the HBeAg-Negative trial.

5.2 Collective Evidence

In the primary efficacy analysis in Study GS-US-320-0108 the percentage of subjects with HBV DNA<29 IU/mL at Week 48 was 94% in the TAF 25 mg arm and 93% in the TDF 300 mg arm. The corresponding risk difference was +1.7% in favor of TAF with 95% CI of -4% to +7%. Therefore it appeared that NI was demonstrated as the lower bound of the 95% CI was much

larger than the NI margin of -10% although for the primary efficacy endpoint TAF was observed to be less efficacious than TDF in subjects with higher viral loads.

In the primary efficacy analysis in Study GS-US-320-0110 the percentage of subjects with HBV DNA<29 IU/mL at Week 48 was 64% in the TAF 25 mg arm and 67% in the TDF 300 mg arm. The corresponding risk difference was -3.5% in favor of TDF with the 95% CI ranging from -9.7% to +2.6%. Therefore since the lower bound of the 95% CI appeared to be slightly larger than the NI margin of -10%, Gilead concluded that NI was demonstrated. However since the two trials did not demonstrate homogeneity of the treatment effect in subjects low and high viral loads, the conclusion of NI of TAF to TDF may only be valid for subjects with lower viral loads of <7 $\log_{10}$ IU/mL.

When the cutoff of 7 $\log_{10}$ IU/mL was used for study GS-US-320-0110 the Zelen test for the treatment by baseline HBV DNA interaction for ALT normalization (using the AASLD criteria) was statistically significant (p=0.006) at the 0.05 level. For subjects with baseline HBV DNA<7 $\log_{10}$ IU/mL the difference between TAF and TDF was 26% (favoring TAF) while there was no statistically significant difference between the two treatment groups for subjects with baseline viral loads ≥7 $\log_{10}$ IU/mL.

5.3 Conclusions and Recommendations

For both trials, the applicant concluded that TAF was not inferior to TDF since the lower bound of the 2-sided 95% CI of the difference (TAF group–TDF group) in the proportion of subjects who achieved HBV DNA < 29 IU/mL at Week 48 was greater than −10%. However in both trials, particularly in Study GS-US-320-0110, homogeneity of the TAF treatment effect appeared to be questionable for baseline viral load, a key baseline covariate used as a stratification variable at randomization.

Although the analysis plan did not pre-specify that the applicant would include the same stratification variables for the two phase 3 trials (using baseline HBV DNA strata of <7, 7 to <8 and ≥8 $\log_{10}$ IU/mL for Study GS-US-320-0108 and <8 and ≥8 $\log_{10}$ IU/mL for Study GS-US-320-0110), this is not a good argument against not using an appropriate cut-off or an adequate range of baseline viral loads to assess the homogeneity of the treatment effect in Study GS-US-320-0110 . Since baseline VL is a continuous variable, the applicant could have included three categories as they did for Study GS-US-320-108, included four categories, or performed sensitivity analyses using different cut-points for dichotomizing baseline viral load. In addition from the reviewer's analyses, it appears that 7 log10 IU/mL is where the shift occurred (from favoring TAF to favoring TDF).

Furthermore although type I error is not strictly controlled for in these subgroup analyses, homogeneity of treatment effect across the most important baseline stratification variables should be demonstrated in order for the applicant to be able to claim that their product works for the entire population of subjects. This does not appear to be the case for subjects with higher baseline viral loads and the label should reflect this finding.

5.4 Labeling Recommendations (as applicable)

Table 47: Proposed table for Section 14 of the label

HBV DNA [redacted] at Week 48[a]

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	[TRADENAME] (N=285)	[redacted] (N=140)	**[TRADENAME]** (N=581)	[redacted] (N=292)
HBV DNA <29 IU/mL	94%	93%	64%	67%
Treatment Difference[b]	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	2%	3%	31%	30%
No Virologic Data at Week 48	4%	4%	5%	3%
[redacted]				
HBV DNA <29 IU/mL By Baseline HBV DNA (log_{10} IU/mL)				
<7	*96%*	*92%*	*88%*	*78%*
≥7	*85%*	*96%*	*55%*	*63%*

a. Missing = failure analysis
b. Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.
c. Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Source: Table 6 of the label and reviewer's analysis

The response rates for subjects in both treatment arms in each trial are shown Table 6 in Section 14 of the draft label. The review team would also like to show efficacy by baseline HBV DNA, as shown by adding an additional two rows at the bottom of the table. Alternatively three strata could be added (e.g., <6, 6 to <7 and ≥7 $\log_{10}$ IU/mL).

APPENDICES

Multiplicity Adjustments for Secondary Efficacy Endpoints

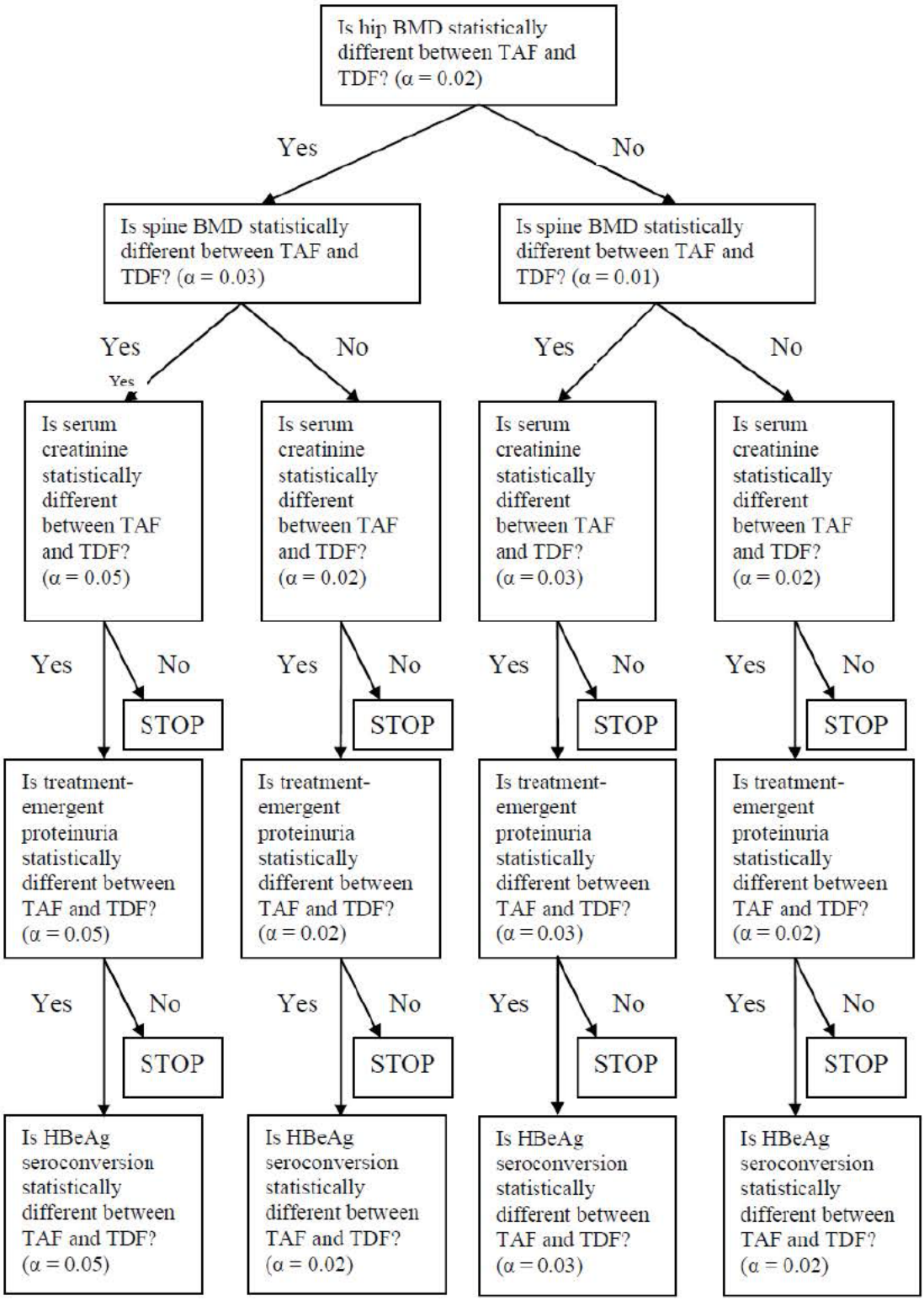
In the SAP the applicant stated the following: To control for Type I error in the assessment of the primary efficacy endpoint and the key secondary safety and efficacy endpoints, the hypothesis testing will be performed in a sequential order.

The primary hypothesis of noninferiority of TAF relative to TDF with respect to the proportion of subjects with HBV DNA < 29 IU/mL at Week 48 will be tested first. Noninferiority test will be performed at one-sided, 0.025 alpha level. If noninferiority is established, multiplicity adjustments will be performed for the following key secondary safety endpoints with a fallback procedure in the sequential order using the following weights with pre-specified 2-sided alpha levels:

a) Hip BMD (weight = 0.4, alpha = 0.02)
b) Spine BMD (weight = 0.2, alpha = 0.01)
c) Serum creatinine (weight = 0.4, alpha = 0.02)
d) Treatment-emergent proteinuria (weight = 0, alpha = 0)
e) HBeAg loss and seroconversion (weight = 0, alpha = 0) (Study GS-US-320-0110 only)

The sequential order of hypothesis testing using the fallback procedure is shown in Figure 3-1 of the Clinical Study Report.

Figure 24: Flowchart of the Fallback Procedure



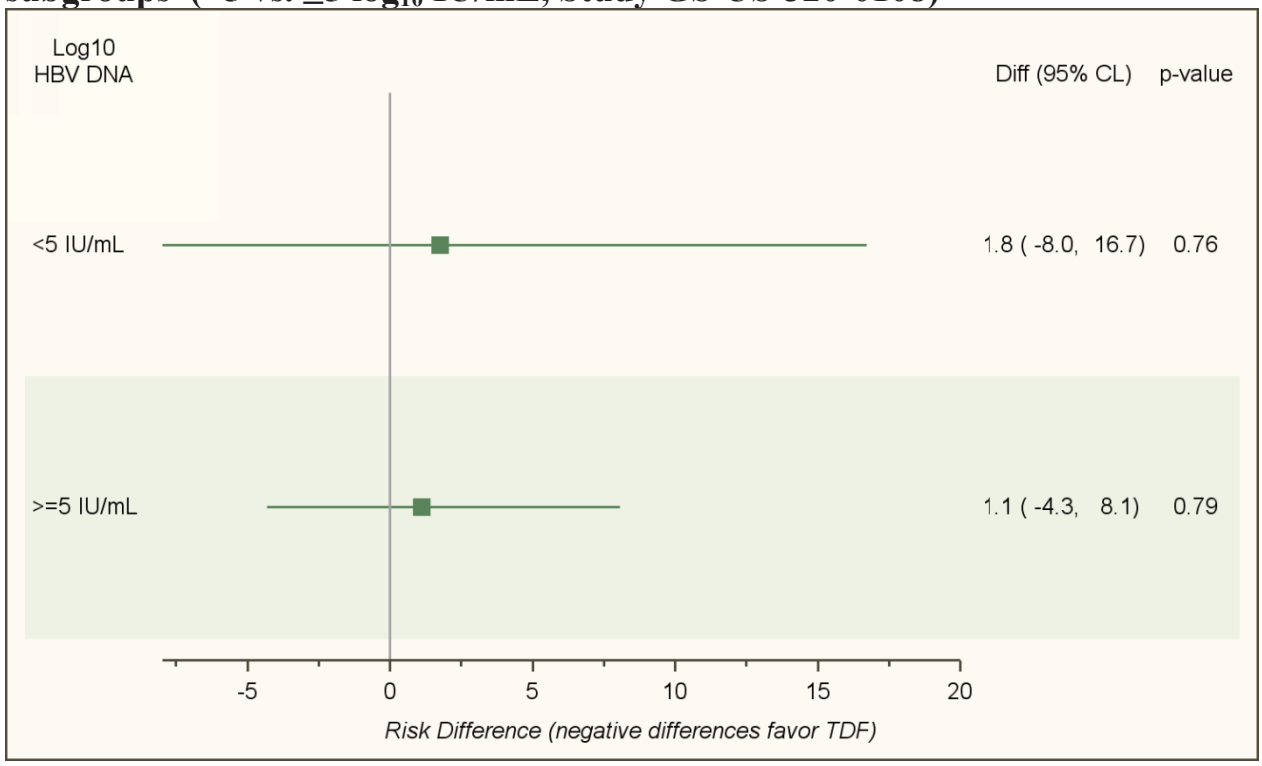
Note that the last row in the flow diagram pertains only to Study GS-US-320-0110
Source: Figure 3-1 of the SAP

Table 48: Analysis Windows for HBV DNA, Hematology, Serum Chemistry and Liver Function Tests, Urinalysis, Urine Pregnancy Test, eGFR (by CG and CKD-EPI), PTH, UACR, UPCR, TmP/GFR, FEPO4, FEUA, Weight, and Vital Sign Assessments (the same windows for both studies)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	69
Week 12	84	70	97
Week 16	112	98	125
Week 20	140	126	153
Week 24	168	154	181
Week 28	196	182	209
Week 32	224	210	237
Week 36	252	238	265
Week 40	280	266	293
Week 44	308	294	321
Week 48	336	322	363
Week 56	392	364	419
Week 64	448	420	475
Week 72	504	476	531
Week 80	560	532	587
Week 88	616	588	643
Week 96	672	644	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1049

Source: Table 3-2 of the SAP

Figure 25: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<5 vs. ≥5 log_{10} IU/mL, Study GS-US-320-0108)



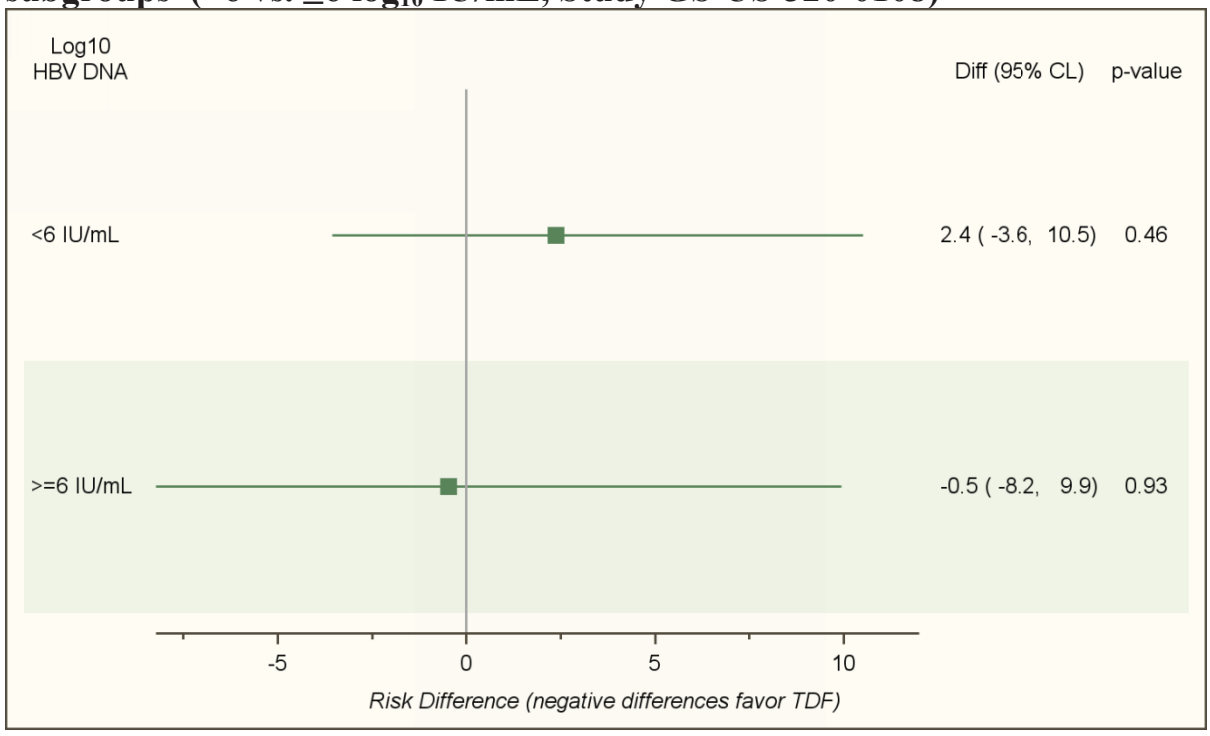
Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=1.00

Table 49: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<5 vs. ≥5 log_{10} IU/mL, Study GS-US-320-0108)

	TAF 25mg (Total=285)		TDF 300mg (Total=140)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<5 IU/mL	85	79 (92.9)	34	31 (91.2)
>=5 IU/mL	200	189 (94.5)	106	99 (93.4)

Source: Statistical Analyst's table with input from the Reviewer

Figure 26: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<6 vs. ≥6 log_{10} IU/mL, Study GS-US-320-0108)



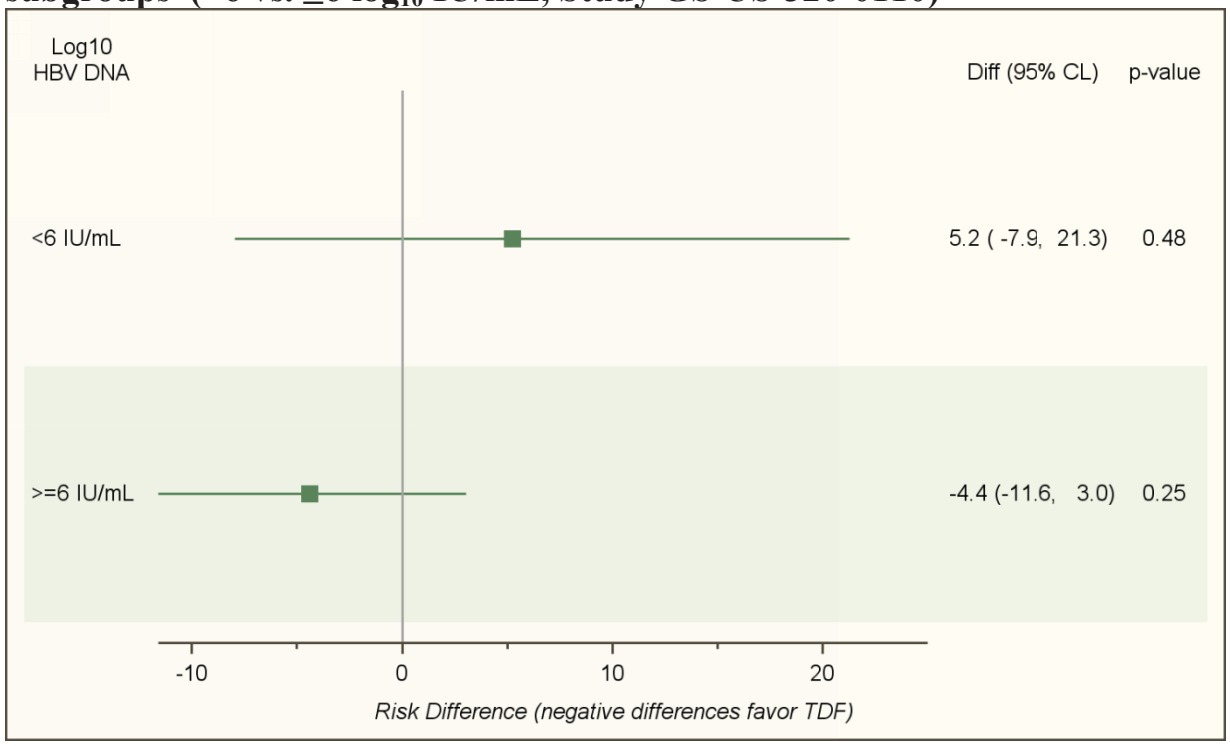
Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=0.69

Table 50: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<6 vs. ≥6 log_{10} IU/mL, Study GS-US-320-0108)

	TAF 25mg (Total=285)		TDF 300mg (Total=140)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<6 IU/mL	165	157 (95.2)	83	77 (92.8)
>=6 IU/mL	120	111 (92.5)	57	53 (93.0)

Source: Statistical Analyst's table with input from the Reviewer

Figure 27: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<6 vs. ≥6 log_{10} IU/mL, Study GS-US-320-0110)



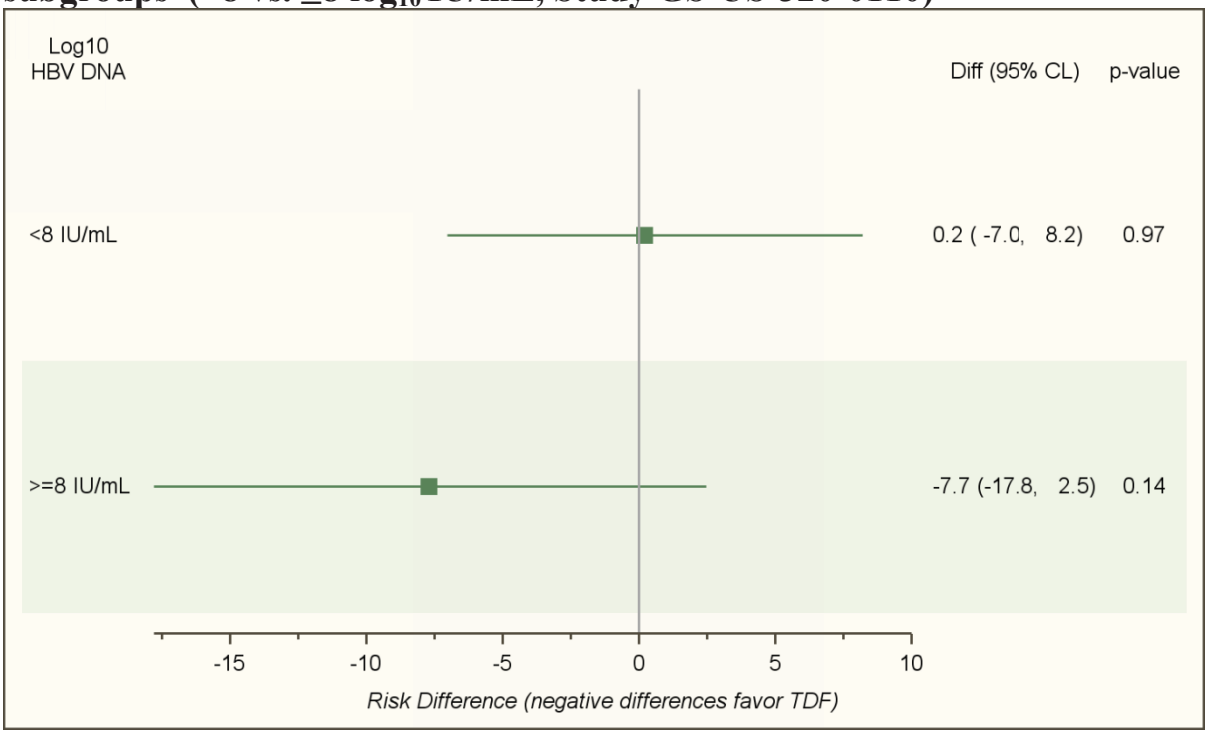
Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=0.28

Table 51: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<6 vs. ≥6 log_{10} IU/mL, Study GS-US-320-0108)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<6 IU/mL	84	72 (85.7)	41	33 (80.5)
>=6 IU/mL	497	299 (60.2)	251	162 (64.5)

Source: Statistical Analyst's table with input from the Reviewer

Figure 28: Forest Plot of Risk Differences for subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<8 vs. ≥8 log_{10} IU/mL, Study GS-US-320-0110)



Source: Statistical Analyst's graph with input from the Reviewer
p-value from Zelen's test=0.40

Table 52: Percentage of subjects with HBV DNA <29 IU/mL at Week 48 (TAF-TDF) using dichotomous baseline HBV DNA subgroups (<8 vs. ≥8 log_{10} IU/mL, Study GS-US-320-0110)

	TAF 25mg (Total=581)		TDF 300mg (Total=292)	
log_{10} HBV DNA	**N**	**n (%)**	**N**	**n (%)**
<8 IU/mL	309	254 (82.2)	150	123 (82.0)
>=8 IU/mL	272	117 (43.0)	142	72 (50.7)

Source: Statistical Analyst's graph with input from the Reviewer

Table 53: Homogeneity Test of Treatment Effect Across Regions for the Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 (Missing = Failure), Full Analysis Set (Study GS-US-320-0108)

	TAF 25mg (N=285)	TDF 300mg (N=140)	TAF 25mg vs. TDF 300mg p-value	TAF 25mg vs. TDF 300mg Odds Ratio (95% CI)
Overall	268 (94.0%)	130 (92.9%)	0.25	1.18 (0.53 to 2.66)
East Asia	110/114 (96.5%)	58/64 (90.6%)		2.84 (0.77 to 10.49)
Europe	69/73 (94.5%)	35/36 (97.2%)		0.49 (0.05 to 4.58)
North America	46/53 (86.8%)	28/30 (93.3%)		0.47 (0.09 to 2.42)
Other	43/45 (95.6%)	9/10 (90.0%)		2.39 (0.19 to 29.27)

Week 48 window is between Day 322 and 363 (inclusive).
Refer to Table 1 for region categorization information.
For overall, the odds ratio and its 95% CI were calculated based on the common odds ratio estimate from the CMH method.
For each region, the odds ratio and its 95% CI were calculated from the CMH method.
P-value for the homogeneity test was based on the Breslow-Day test of the interaction between treatment and region.

Source: Table 16 of the Clinical Study Report

Table 54: Homogeneity Test of Treatment Effect Across Regions in Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 (Missing = Failure), Full Analysis Set (Study GS-US-320-0110)

	TAF 25mg (N=581)	TDF 300mg (N=292)	TAF 25mg vs. TDF 300mg p-value	TAF 25mg vs. TDF 300mg Odds Ratio (95% CI)
Overall	371 (63.9%)	195 (66.8%)	0.48	0.87 (0.65 to 1.18)
East Asia	208/287 (72.5%)	110/145 (75.9%)		0.84 (0.53 to 1.33)
Europe	54/104 (51.9%)	24/53 (45.3%)		1.31 (0.67 to 2.53)
North America	51/88 (58.0%)	30/49 (61.2%)		0.87 (0.43 to 1.78)
Other	58/102 (56.9%)	31/45 (68.9%)		0.60 (0.28 to 1.25)

Week 48 window is between Day 322 and 363 (inclusive).
Refer to Table 1 for region categorization information.
For overall, the odds ratio and its 95% CI were calculated based on the common odds ratio estimate from the CMH method.
For each region, the odds ratio and its 95% CI were calculated from the CMH method.
P-value for the homogeneity test was based on the Breslow-Day test of the interaction between treatment and region.

Source: Table 16 of the Clinical Study Report

Table 55: Homogeneity Test of Treatment Effect Between Subgroups for the Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 (Missing = Failure), Full Analysis Set (Study GS-US-320-0108)

	TAF 25mg (N=285)	TDF 300mg (N=140)	TAF 25mg vs. TDF 300mg p-value	TAF 25mg vs. TDF 300mg Odds Ratio (95% CI)
Age (Years)				
< 50	171/176 (97.2%)	64/69 (92.8%)	0.057	2.99 (0.83 to 10.82)
>= 50	97/109 (89.0%)	66/71 (93.0%)		0.57 (0.19 to 1.72)
Sex				
Male	162/173 (93.6%)	80/86 (93.0%)	0.68	1.09 (0.39 to 3.08)
Female	106/112 (94.6%)	50/54 (92.6%)		1.55 (0.41 to 5.79)
Race				
Asian	192/205 (93.7%)	92/101 (91.1%)	0.33	1.54 (0.63 to 3.78)
Non-Asian	76/80 (95.0%)	38/39 (97.4%)		0.47 (0.05 to 4.41)
Baseline HBV DNA				
< 7 log10 IU/mL	221/230 (96.1%)	107/116 (92.2%)	0.080	2.07 (0.80 to 5.36)
>= 7 log10 IU/mL	47/55 (85.5%)	23/24 (95.8%)		0.26 (0.03 to 2.17)
Oral Antiviral Treatment Status				
Treatment Experienced	56/60 (93.3%)	28/30 (93.3%)	0.82	1.03 (0.18 to 6.06)
Treatment Naive	212/225 (94.2%)	102/110 (92.7%)		1.31 (0.52 to 3.28)
Region				
East Asia	110/114 (96.5%)	58/64 (90.6%)	0.089	3.06 (0.82 to 11.39)
Non-East Asia	158/171 (92.4%)	72/76 (94.7%)		0.66 (0.21 to 2.12)

Region				
Europe	69/73 (94.5%)	35/36 (97.2%)	0.36	0.49 (0.05 to 4.57)
Non-Europe	199/212 (93.9%)	95/104 (91.3%)		1.51 (0.62 to 3.69)
Region				
North America	46/53 (86.8%)	28/30 (93.3%)	0.18	0.48 (0.09 to 2.50)
Non-North America	222/232 (95.7%)	102/110 (92.7%)		1.79 (0.68 to 4.70)
Study Drug Adherence (%)				
< 95	3/4 (75.0%)	5/6 (83.3%)	0.59	0.50 (0.02 to 11.73)
>= 95	265/281 (94.3%)	125/134 (93.3%)		1.23 (0.53 to 2.87)
Genotype				
A/D	98/105 (93.3%)	46/48 (95.8%)	0.25	0.59 (0.12 to 2.96)
B/C	165/175 (94.3%)	79/87 (90.8%)		1.77 (0.67 to 4.70)
Baseline ALT by Central Lab Normal Range				
<= ULN	46/49 (93.9%)	17/19 (89.5%)	0.60	2.00 (0.30 to 13.15)
> ULN	222/236 (94.1%)	113/121 (93.4%)		1.15 (0.47 to 2.84)
Baseline Fibrotest Score				
< 0.75	237/249 (95.2%)	110/119 (92.4%)	0.13	1.80 (0.72 to 4.45)
>= 0.75	27/31 (87.1%)	19/20 (95.0%)		0.26 (0.03 to 2.59)

Week 48 window is between Day 322 and 363 (inclusive).
Odds ratio and its 95% CIs were estimated for each subgroup from the logistic regression model including baseline HBV DNA categoreis and oral antiviral treatment status (if not the subgroup factor), subgroup, treatment, and the interaction between treatment and subgroup.
For this subgroup analysis, 2-level baseline HBV DNA categories (< 7 log10 IU/mL and >= 7 log10 IU/mL) were used.
P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup.
Study drug adherence subgroups analysis are based on the adherence up to Week 48 visit for active study drug.

Source: Table 17.2 of the Clinical Study Report

Table 56: Homogeneity Test of Treatment Effect Between Subgroups for the Percentage of Subjects with HBV DNA < 29 IU/mL at Week 48 (Missing = Failure), Full Analysis Set (Study GS-US-320-0110)

	TAF 25mg (N=581)	TDF 300mg (N=292)	TAF 25mg vs. TDF 300mg p-value	TAF 25mg vs. TDF 300mg Odds Ratio (95% CI)
Age (Years)				
< 50	313/493 (63.5%)	161/234 (68.8%)	0.11	0.73 (0.50 to 1.04)
>= 50	58/88 (65.9%)	34/58 (58.6%)		1.43 (0.68 to 3.03)
Sex				
Male	228/371 (61.5%)	120/189 (63.5%)	0.20	0.96 (0.65 to 1.43)
Female	143/210 (68.1%)	75/103 (72.8%)		0.61 (0.35 to 1.09)
Race				
Asian	321/482 (66.6%)	162/232 (69.8%)	0.93	0.81 (0.56 to 1.17)
Non-Asian	50/99 (50.5%)	33/60 (55.0%)		0.84 (0.42 to 1.70)
Baseline HBV DNA				
< 8 log10 IU/mL	254/309 (82.2%)	123/150 (82.0%)	0.34	1.01 (0.60 to 1.68)
>= 8 log10 IU/mL	117/272 (43.0%)	72/142 (50.7%)		0.73 (0.49 to 1.11)
Oral Antiviral Treatment Status				
Treatment Experienced	69/137 (50.4%)	39/69 (56.5%)	0.68	0.74 (0.39 to 1.40)
Treatment Naive	302/444 (68.0%)	156/223 (70.0%)		0.86 (0.59 to 1.26)
Region				
East Asia	208/287 (72.5%)	110/145 (75.9%)	0.90	0.85 (0.52 to 1.39)
Non-East Asia	163/294 (55.4%)	85/147 (57.8%)		0.81 (0.53 to 1.26)

Region				
Europe	54/104 (51.9%)	24/53 (45.3%)	0.13	1.37 (0.66 to 2.84)
Non-Europe	317/477 (66.5%)	171/239 (71.5%)		0.73 (0.51 to 1.05)
Region				
North America	51/88 (58.0%)	30/49 (61.2%)	0.83	0.76 (0.35 to 1.66)
Non-North America	320/493 (64.9%)	165/243 (67.9%)		0.84 (0.59 to 1.20)
Study Drug Adherence (%)				
< 95	10/16 (62.5%)	6/9 (66.7%)	0.49	0.42 (0.07 to 2.66)
>= 95	361/565 (63.9%)	189/280 (67.5%)		0.81 (0.58 to 1.13)
Genotype				
A/D	87/173 (50.3%)	46/88 (52.3%)	0.77	0.89 (0.51 to 1.55)
B/C	281/403 (69.7%)	147/200 (73.5%)		0.80 (0.53 to 1.21)
Baseline ALT by Central Lab Normal Range				
<= ULN	26/44 (59.1%)	17/24 (70.8%)	0.82	0.73 (0.23 to 2.32)
> ULN	345/537 (64.2%)	178/268 (66.4%)		0.84 (0.60 to 1.17)
Baseline Fibrotest Score				
< 0.75	332/521 (63.7%)	172/260 (66.2%)	0.90	0.84 (0.60 to 1.18)
>= 0.75	31/45 (68.9%)	17/22 (77.3%)		0.77 (0.21 to 2.78)

Week 48 window is between Day 322 and 363 (inclusive).
Odds ratio and its 95% CIs were estimated for each subgroup from the logistic regression model including baseline HBV DNA categoreis and oral antiviral treatment status (if not the subgroup factor), subgroup, treatment, and the interaction between treatment and subgroup.
P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup.
Study drug adherence subgroups analysis are based on the adherence up to Week 48 visit for active study drug.

Source: Table 17.2 of the Clinical Study Report

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/s/

FRASER B SMITH
10/06/2016

GUOXING SOON
10/06/2016