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 #:	208464
Supplement #:	14 (b) (4)
EDR Location:	\\CDSESUB1\evsprod\NDA208464\0130
Related IND #:	115561
Indication(s):	Treatment of chronic hepatitis B virus (HBV) infection in (b) (4) adolescent
Applicant:	Gilead Sciences, Inc.
Dates:	Received: 4/19/2022 PDUFA: 10/19/2022
Review Priority:	Priority Review (6 months)
Biometrics Division:	Division of Biometrics (DB) IV
Statistical Reviewer:	Yifan Wang, Ph.D., DB VIII
Concurring Reviewers:	Somesh Chattopadhyay, Ph.D., DB VIII (Statistics Team Lead)
Tertiary Reviewers:	Thamban Valappil, Ph.D., DB IV (Statistics Team Lead)
Medical Division:	Division of Antivirals (DAV)
Clinical Team:	Jency Daniel, MD Samer El-Kamay, MD/Prabha Viswanathan, MD (CDTL)
Project Manager:	Myung-Joo P. Hong
Keywords:	Phase 2, interim clinical study, Cohort 1 (adolescents 12 to < 18 years, ≥ 35 kg), Cohort 2 Group 1 (children 2 to < 12 years, ≥ 25 kg), HBV, proportion of participants with HBV deoxyribonucleic acid (DNA) <20 IU/mL, superiority, Cochran-Mantel-Haenszel (CMH) test

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Vemlidy® (tenofovir alafenamide; TAF) was approved by the Agency on 11/10/2016 for the treatment of chronic hepatitis B (CHB) virus infection in adults with compensated liver disease. Gilead Sciences, Inc. (Gilead) submitted the supplemental New Drug Application (sNDA) S14 (b) (4) to NDA 208464 as an efficacy supplement with the interim clinical study report for the pediatric study GS-US-320-1092 in support of proposed labeling changes to the approved Vemlidy US prescribing information (USPI), and in response to the pediatric Written Request (WR) issued on 12/19/2014 to investigate the potential use of TAF in the treatment of pediatric patients 2 to < 18 years of age.

Study GS-US-320-1092 (Phase 2) is an ongoing randomized (2:1), double-blind, placebo-controlled, multicenter study of the Pharmacokinetics (PK), safety, and antiviral efficacy of TAF in children and adolescent subjects with chronic hepatitis B virus (HBV) infection.

Table 1 presents a summary of the primary endpoint analysis findings at Week 24. The results show that TAF is superior to the placebo for the treatment of chronic HBV infection in the combined cohorts of Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg) and Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg), demonstrated by *p*-value = 0.0137 of Cochran-Mantel-Haenszel (CMH) test adjusted for age at baseline. Please note that the CMH *p*-value is unavailable for Cohort 2 Group 1 due to the small sample size and lack of power. The results for children (aged 6 to < 12 years old weighing ≥ 25 kg) should be used with caution.

Table 1: Primary Efficacy Endpoint Analysis for Proportion of Participants with HBV DNA < 20 IU/mL at Week 24 (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

HBV DNA <20 IU/mL at Week 24	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
Proportion	10/47 (21.3%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	11/59 (18.6%)	0/29 (0%)
95% CI	(10.7%, 35.7%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(9.7%, 30.9%)	(0%, 11.9%)
Proportion difference	21.3%		8.3%		18.6%	
95% CI for difference	(6.3%, 36.2%)		(-19.8%, 36.5%)		(5.4%, 31.6%)	
p-value	0.0199		.		0.0137	

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline.
95% CIs were calculated using the Clopper-Pearson method.
Source: Reviewer's Analysis

2. INTRODUCTION

2.1 Overview

TAF was approved by the US Food and Drug Administration (FDA) for the treatment of chronic HBV infection in adults with compensated liver disease on 11/10/2016, based on the efficacy and safety results from two registration studies (GS-US-320-0108 and GS-US-320-0110) conducted in viremic adult participants with elevated alanine aminotransferase (ALT) values in NDA 208464. The two studies used a 25 mg dose of TAF and demonstrated noninferior efficacy of TAF compared with tenofovir disoproxil fumarate (TDF) in the proportion of participants with HBV deoxyribonucleic acid (DNA) < 29 IU/mL at Week 48.

The current submission of the supplemental NDA (S14 (b) (4) provided efficacy results of an interim analysis at Week 24 for participants aged 12 to < 18 years weighing ≥ 35 kg (Cohort 1), and participants aged 6 to < 12 years weighing ≥ 25 kg (Cohort 2 Group 1). The primary efficacy endpoint was the percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24.

2.2 Data Sources

The data were submitted electronically and are located in

\\Cdsesub1\evsprod\NDA208464\0130\m5\datasets\gs-us-320-1092\analysis\adam\datasets

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data in this NDA is acceptable, and the reviewer was able to access the information.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

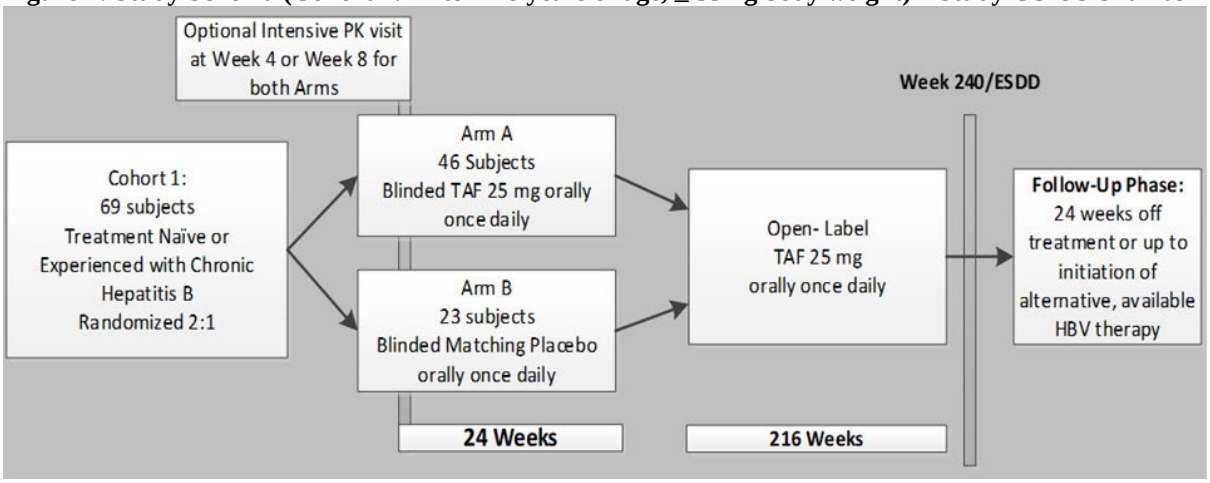
Study GS-US-320-1092 (Phase 2) is an ongoing randomized (2:1), double-blind, placebo-controlled, multicenter (36 sites in Belgium, Hong Kong, India, New Zealand, Romania, Russia, South Korea, Taiwan, and United States) study of the Pharmacokinetics (PK), safety, and antiviral efficacy of TAF in children and adolescent subjects with chronic HBV infection.

The current submission of the supplemental NDA (S14 (b) (4) focused on the results of an interim analysis for participants aged 12 to < 18 years weighing ≥ 35 kg (Cohort 1), and participants aged 6 to < 12 years weighing ≥ 25 kg (Cohort 2 Group 1), who were receiving the adult dose of TAF 25 mg or the placebo once daily. The interim analysis was performed when all participants in Cohort 1 and Cohort 2 Group 1 had completed their Week 24 visit or prematurely discontinued from the study. Following double-blind treatment for 24 weeks, all participants were eligible to roll over to receive open-label TAF for a total duration of study treatment of 240 weeks.

Cohort 1:

At least 69 male and female adolescent participants (12 to < 18 years of age) were planned to be enrolled and randomized to receive either the blinded TAF 25 mg tablet or placebo tablet once daily through Week 24. Randomization was stratified by age (12 to < 15 and 15 to < 18 years of age). Adolescent participants who were enrolled were eligible to take part in an optional intensive PK substudy that was performed at either the Week 4 visit (± 7 days) or the Week 8 visit (± 7 days). For participants who consented to participate in the optional intensive PK substudy, blood samples were collected at 0 (predose, ≤ 30 minutes prior to dosing), 15, and 30 minutes, and 1, 1.5, 2, 3, 4, 5, and 8 hours postdose.

Figure 1: Study Schema (Cohort 1: 12 to < 18 years of age, ≥ 35 kg body weight) – Study GS-US-320-1092



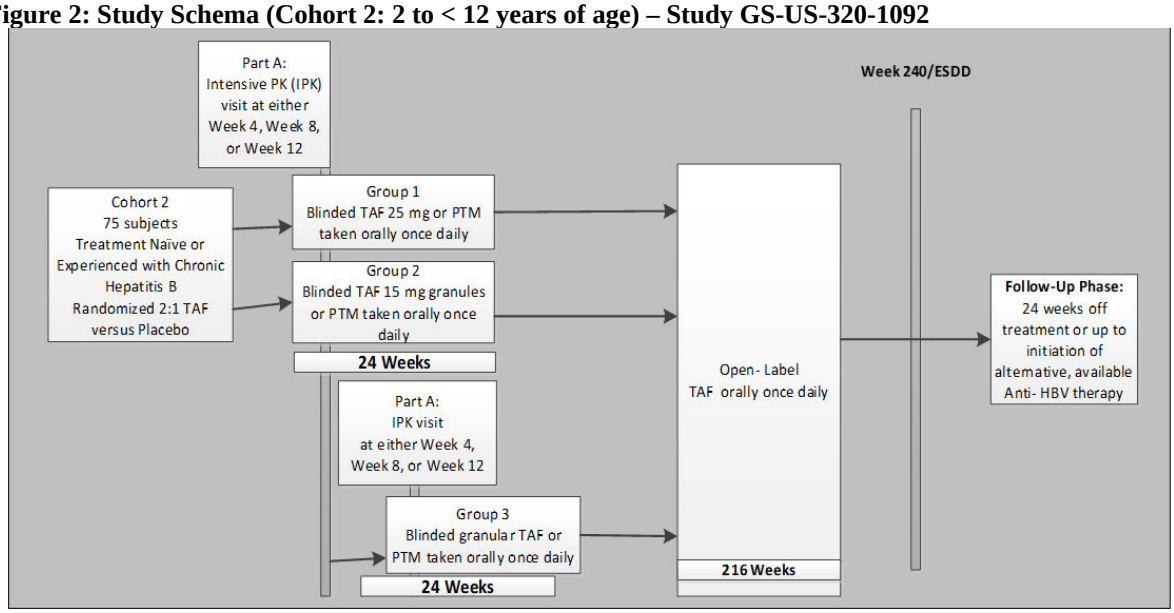
Source: Applicant's Clinical Study Report Figure 1, Page 34/642

Cohort 2:

At least 75 children were planned to be enrolled in Cohort 2 of the study. Cohort 2 was divided into three dose groups (Groups 1, 2, and 3) by age and weight, with enrollment into each dose group divided into two parts without overlapping: Part A (mandatory intensive PK to confirm the dose) and Part B. Intensive PK data were to be collected from participants in Part A to confirm the dose of TAF in each dose group and the remaining participants were planned to be enrolled into Part B once dose confirmation was achieved. Part A was planned with a minimum of 27 enrolled participants (a minimum of 6, 9, and 12 participants in Groups

1, 2, and 3, respectively) and Part B was planned to have at least 48 enrolled participants across all 3 groups.

Figure 2: Study Schema (Cohort 2: 2 to < 12 years of age) – Study GS-US-320-1092



Source: Applicant's Clinical Study Report Figure 2, Page 35/642

- **Cohort 2 Part A**: Enrollment and dosing for Cohort 2 Part A was planned as follows.

Table 2: Enrollment and Dosing for Cohort 2 Part A (Intensive PK Evaluation for Confirming the Dose) – Study GS-US-320-1092

Group	Age Range	Weight Range	TAF Dose	Number of Participants
Group 1	6 to < 12 years	≥ 25 kg (≥ 55 lbs)	25 mg tablet	n = 6
Group 2[b]	6 to < 12 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 9
Group 3[b]	2 to < 6 years	≥ 14 kg to < 25 kg (≥ 30 lbs to < 55 lbs)	15 mg oral granules (2 × TAF 7.5 mg oral granules)	n = 12 at least 6 participants weighing ≥ 10 to < 14 kg
		≥ 10 kg to < 14 kg (≥ 22 lbs to < 30 lbs)	7.5 mg oral granules	

TAF = tenofovir alafenamide; PK = pharmacokinetic(s)
a All participants in Cohort 2 Part A were to undergo a mandatory intensive PK evaluation at either Week 4 visit (± 7 days), Week 8 visit (± 7 days), or Week 12 visit (± 7 days) to confirm the dose of TAF. Cohort 2 Part B is identical to Cohort 2 Part A in design, without an intensive PK requirement.
b Results from Cohort 2 Groups 2 and 3 will be reported separately.

Source: Applicant's Clinical Study Report Table 2, Page 35/642

- **Cohort 2, Part B**: Cohort 2, Part B is identical to Cohort 2, Part A in design, without the inclusion of an intensive PK requirement. Screening was planned to be initiated for Cohort 2, Part B (Groups 1 and 2) following confirmation of the TAF dose in Part A for each group, respectively. Screening will be initiated for Cohort 2, Part B (Group 3) following confirmation of the clinical safety and PK results of the TAF dose from

Cohort 2, Part A (Groups 1, 2, and 3). Participants who participated in Cohort 2 Part A were not planned to be rolled over into Cohort 2, Part B. Approximately 48 additional participants were planned for enrollment in Part B across all 3 groups to evaluate the safety, tolerability, and antiviral activity of TAF in a total of 75 participants in Parts A and B combined.

A brief outline of Study GS-US-320-1092 is presented in Table 3.

Table 3: Summary of Trials to be Assessed in the Statistical Review – Study GS-US-320-1092

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
GS-US-320-1092	Randomized (2:1), double-blind, placebo-controlled, multicenter	TAF 25mg / FAS: Cohort 1 N=47 Cohort 2 Group 1 N=12 Total N=59 Placebo / FAS: Cohort 1 N=23 Cohort 2 Group 1 N=6 Total N=29 Total N=88	Primary endpoint: Proportion of subjects with HBV DNA <20 IU/mL at Week 24 Analysis: The superiority of TAF over placebo for the proportion of HBV DNA < 20 IU/mL was tested using stratified Cochran-Mantel-Haenszel (CMH) test adjusted for age at baseline.	Overall, the proportion of participants with HBV DNA <20 IU/mL was 18.6% (11 of 59 participants) with TAF versus 0.0% (0 of 29 participants) with placebo (*p*-value = 0.0137) at Week 24. Gilead concluded that the antiviral response with TAF treatment is superior to placebo.

FAS: Full Analysis Set, which included all participants who were randomized into the study and received at least one dose of study drug.
Source: Reviewer's Table using results from the Clinical Study Report

3.2.2 Statistical Methodology

The primary efficacy analysis was conducted after the last randomized participant reached Week 24 or discontinued study drug prematurely. The primary efficacy analysis used the Full Analysis Set (FAS), which included all participants who were randomized into the study and received at least one dose of study drug. The primary efficacy endpoint analysis compared the difference in the proportion of participants with HBV DNA < 20 IU/mL (by missing equals failure [M = F] analysis) at Week 24 between treatment with TAF and placebo using the following hypotheses:

Null: the difference (TAF - placebo) in the proportions of subjects with HBV DNA < 20 IU/mL at Week 24 = 0

Alternative: the difference (TAF - placebo) in the proportions of subjects with HBV DNA < 20 IU/mL at Week 24 ≠ 0

The superiority of TAF over placebo for the proportion of HBV DNA < 20 IU/mL was tested using stratified Cochran-Mantel-Haenszel (CMH) test adjusted for age at baseline.

The analysis of the proportion of participants with plasma HBV DNA < 20 IU/mL at Week 24 was repeated within each subgroup.

Secondary efficacy endpoints evaluated for the Week 24 analysis included additional analysis of HBV DNA and analyses of ALT, liver fibrosis (by serum FibroTest), hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) serology, virological resistance, and acceptability/palatability analysis using the FAS, unless otherwise specified.

For the primary and secondary efficacy endpoints involving proportions, missing data was handled using the missing equals failure approach.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 161 participants were screened for this study; 73 participants failed screening, including 3 participants who met all eligibility criteria but were not randomized due to COVID-19 resulting in temporary halt of enrolment (one participant) or withdrawal of consent (two participants). Of the 161 participants screened, 88 were randomized (Cohort 1 TAF 47 participants, placebo 23 participants; Cohort 2 Group 1 TAF 12 participants, placebo six participants). All participants who were randomized received study drug or placebo.

The 88 participants were randomized and treated at 36 study centers in the following countries/regions: one in Belgium, two in Hong Kong, 12 in India, one in New Zealand, five in Romania, 17 in Russia, eight in South Korea, eight in Taiwan, and 34 in the US.

Table 4 presents the participant disposition. All 88 participants who were randomized completed the double-blind study treatment. No participants discontinued study drug or the study during the double-blind phase.

Table 4: Disposition of Participants (All Screened Participants) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total		
	TAF 25mg	Placebo	TAF 25mg	Placebo	TAF 25mg	Placebo	Overall
Screened							161
Screen failure participants who were not randomized							73
Participants who met all eligibility criteria and were not randomized							3
COVID-19 resulted in temporary halt of enrollment							1
Withdrew consent							2
Randomized Analysis Set	47	23	12	6	59	29	88
Safety Analysis Set	47	23	12	6	59	29	88
Full Analysis Set	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Per Protocol Analysis Set	44 (93.6%)	23 (100.0%)	11 (91.7%)	5 (83.3%)	55 (93.2%)	28 (96.6%)	83 (94.3%)
Double-Blind Phase							
Completed Double-Blind drug	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)	88 (100.0%)
Continuing	0	0	0	0	0	0	0
Prematurely discontinued	0	0	0	0	0	0	0

COVID-19 = coronavirus disease 2019; TAF = tenofovir alafenamide
Denominator for percentages was the Safety Analysis Set.
Source: Applicant's Clinical Study Report Table 7, Page 77/642

Table 5 and 6 summarize participant demographics and other baseline characteristics. Demographic and baseline characteristics were generally similar between the two treatment groups. The majority of participants were male (58%) and Asian (65.9%).

Table 5: Demographic Characteristics (Safety Analysis Set) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
Age (years)						
N	47	23	12	6	59	29
Mean (SD)	15 (1.9)	15 (1.5)	10 (1.3)	8 (0.8)	14 (2.7)	13 (3.0)
Median (min, max)	15 (12, 17)	15 (12, 17)	10 (7, 11)	8 (7, 9)	14 (7, 17)	14 (7, 17)
Sex						
Female	20 (42.6%)	7 (30.4%)	5 (41.7%)	5 (83.3%)	25 (42.4%)	12 (41.4%)
Male	27 (57.4%)	16 (69.6%)	7 (58.3%)	1 (16.7%)	34 (57.6%)	17 (58.6%)
Race						
Asian	33 (70.2%)	18 (78.3%)	4 (33.3%)	3 (50.0%)	37 (62.7%)	21 (72.4%)
Black or African American	2 (4.3%)	2 (8.7%)	1 (8.3%)	0	3 (5.1%)	2 (6.9%)
Native Hawaiian or Other Pacific Islander	1 (2.1%)	0	0	0	1 (1.7%)	0
Other	2 (4.3%)	0	0	0	2 (3.4%)	0
White	9 (19.1%)	3 (13.0%)	7 (58.3%)	3 (50.0%)	16 (27.1%)	6 (20.7%)
Ethnicity						
Hispanic or Latino	2 (4.3%)	0	0	0	2 (3.4%)	0
Not Hispanic or Latino	44 (93.6%)	22 (95.7%)	12 (100.0%)	6 (100.0%)	56 (94.9%)	28 (96.6%)
Not permitted	1 (2.1%)	1 (4.3%)	0	0	1 (1.7%)	1 (3.4%)
Weight (kg)						
N	47	23	12	6	59	29
Mean (SD)	54.0 (10.74)	56.5 (10.96)	37.9 (7.96)	30.8 (4.97)	50.7 (12.09)	51.2 (14.53)
Median (min, max)	54.6 (36.3, 87.5)	55.8 (35.0, 78.5)	37.1 (29.0, 54.1)	32.2 (24.0, 36.5)	52.2 (29.0, 87.5)	52.0 (24.0, 78.5)
Height (cm)						
N	47	23	12	6	59	29
Mean (SD)	161.8 (9.74)	164.6 (9.95)	141.4 (9.14)	136.8 (5.11)	157.6 (12.63)	158.8 (14.62)
Median (min, max)	160.5 (143.0, 183.0)	166.5 (144.8, 179.5)	140.2 (125.0, 155.0)	136.4 (130.0, 144.0)	156.4 (125.0, 183.0)	161.3 (130.0, 179.5)
Body Mass Index (kg/m^2)						
N	47	23	12	6	59	29
Mean (SD)	20.5 (2.89)	20.7 (2.57)	18.8 (2.70)	16.4 (2.16)	20.2 (2.91)	19.8 (3.02)
Median (min, max)	20.4 (15.5, 29.4)	20.3 (16.0, 27.3)	18.2 (15.8, 24.3)	16.4 (13.6, 19.7)	20.1 (15.5, 29.4)	19.7 (13.6, 27.3)

Body Mass Index (kg/m^2) = [Weight (kg)/Height $(cm)^2$] * 10,000
Source: Reviewer's analysis.

Table 6: Baseline Disease Characteristics (Safety Analysis Set) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
HBV DNA (log10 IU/mL)						
N	47	23	12	6	59	29
Mean (SD)	7.9 (1.13)	8.1 (0.80)	8.0 (1.09)	8.3 (0.28)	7.9 (1.12)	8.1 (0.72)
Median (min, max)	8.1 (2.5, 9.2)	8.3 (5.4, 9.2)	8.1 (5.0, 9.2)	8.3 (7.8, 8.6)	8.1 (2.5, 9.2)	8.3 (5.4, 9.2)
HBsAg (log10 IU/mL)						
N	47	23	12	6	59	29
Mean (SD)	4.4 (0.50)	4.5 (0.57)	4.4 (0.84)	4.7 (0.49)	4.4 (0.58)	4.6 (0.55)
Median (min, max)	4.5 (3.3, 5.1)	4.6 (2.9, 5.1)	4.5 (2.0, 5.1)	4.7 (3.8, 5.1)	4.5 (2.0, 5.1)	4.7 (2.9, 5.1)
HBsAg status						
Positive	47 (100.0%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	59 (100.0%)	29 (100.0%)
HBeAg status						
Negative	1 (2.1%)	0	0	0	1 (1.7%)	0
Positive	46 (97.9%)	23 (100.0%)	12 (100.0%)	6 (100.0%)	58 (98.3%)	29 (100.0%)
ALT (U/L)						
N	47	23	12	6	59	29
Mean (SD)	112 (134.4)	110 (110.5)	85 (69.0)	96 (94.0)	106 (123.9)	107 (105.9)
Median (min, max)	68 (19, 793)	76 (20, 502)	59 (22, 274)	60 (43, 286)	65 (19, 793)	66 (20, 502)
Baseline fibrosis score category						
0.00-0.48	43 (95.6%)	21 (95.5%)	11 (91.7%)	6 (100.0%)	54 (94.7%)	27 (96.4%)
0.49-0.74	2 (4.4%)	1 (4.5%)	1 (8.3%)	0	3 (5.3%)	1 (3.6%)

TAF = tenofovir alafenamide; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; ALT = alanine aminotransferase
Source: Reviewer's analysis.

3.2.4 Results and Conclusions

Primary Efficacy Endpoint Analysis

Table 7 presents the results of the analysis of the primary efficacy endpoint, the percentage of participants with plasma HBV DNA < 20 IU/mL at Week 24, by cohort and treatment group using FAS and missing equals failure approach. The results show that TAF is superior to the placebo for the treatment of chronic HBV infection in the combined cohorts of Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg) and Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg), demonstrated by *p*-value = 0.0137 of Cochran-Mantel-Haenszel (CMH) test adjusted for age at baseline.

For Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg), the proportion of participants with HBV DNA <20 IU/mL was 21.3% (10 of 47 participants) with TAF versus 0.0% (0 of 23 participants) with placebo (*p*-value = 0.0199) at Week 24.

For Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg), the proportion of participants with HBV DNA <20 IU/mL was 8.3% (1 of 12 participants) with TAF versus 0.0% (0 of 6 participants) with placebo (*p*-value cannot be calculated due to the small sample size) at Week 24.

Table 7: Primary Efficacy Endpoint Analysis for Proportion of Participants with HBV DNA < 20 IU/mL at Week 24 (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

HBV DNA <20 IU/mL at Week 24	Cohort 1		Cohort 2 Group 1		Total	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)
Proportion	10/47 (21.3%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	11/59 (18.6%)	0/29 (0%)
95% CI	(10.7%, 35.7%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(9.7%, 30.9%)	(0%, 11.9%)
Proportion difference	21.3%		8.3%		18.6%	
95% CI for difference	(6.3%, 36.2%)		(-19.8%, 36.5%)		(5.4%, 31.6%)	
p-value	0.0199		.		0.0137	

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline.
95% CIs were calculated using the Clopper-Pearson method.
Source: Reviewer's Analysis

Reviewer's Comments:

Please note that the primary efficacy endpoint analysis results for Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg) should be used with caution due to the small sample size (12 participants in the TAF group versus 6 participants in the placebo group) and lack of power.

Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoints analyses included additional analyses of HBV DNA and analyses of ALT, liver fibrosis, HBeAg and HBsAg serology.

Table 8 present the proportion of participants with plasma HBV DNA < 20 IU/mL at baseline, Weeks 4, 8, 12, 16 and 24 by treatment group for the FAS using the M = F approach for missing data. Overall, a consistent increase in the number of participants with HBV DNA < 20 IU/mL was observed in the TAF group, while no increase was observed in the placebo group.

Table 8: Secondary Efficacy Endpoint Analysis for Proportion of Participants with HBV DNA < 20 IU/mL by Visit (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

HBV DNA <20 IU/mL	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo	
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)	*p*-value	Prop Diff (95% CI)
Baseline								
Proportion	0/47 (0%)	0/23 (0%)	0/12 (0%)	0/6 (0%)	0/59 (0%)	0/29 (0%)	N/A	
95% CI	(0%, 7.5%)	(0%, 14.8%)	(0%, 26.5%)	(0%, 45.9%)	(0%, 6.1%)	(0%, 11.9%)		
Week 4								
Proportion	1/47 (2.1%)	0/23 (0%)	0/12 (0%)	0/6 (0%)	1/59 (1.7%)	0/29 (0%)	0.4795	1.7% (-7.9% to 11.3%)
95% CI	(0.1%, 11.3%)	(0%, 14.8%)	(0%, 26.5%)	(0%, 45.9%)	(0%, 9.1%)	(0%, 11.9%)		
Week 8								
Proportion	0/47 (0%)	0/23 (0%)	0/12 (0%)	0/6 (0%)	0/59 (0%)	0/29 (0%)	N/A	
95% CI	(0%, 7.5%)	(0%, 14.8%)	(0%, 26.5%)	(0%, 45.9%)	(0%, 6.1%)	(0%, 11.9%)		
Week 12								
Proportion	1/47 (2.1%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	2/59 (3.4%)	0/29 (0%)	0.3173	3.4% (-6.7% to 13.5%)
95% CI	(0.1%, 11.3%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(0.4%, 11.7%)	(0%, 11.9%)		
Week 16								
Proportion	4/47 (8.5%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	5/59 (8.5%)	0/29 (0%)	0.1118	8.4% (−2.9% to 19.7%)
95% CI	(2.4%, 20.4%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(2.8%, 18.7%)	(0%, 11.9%)		
Week 24								
Proportion	10/47 (21.3%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	11/59 (18.6%)	0/29 (0%)	0.0137	18.5% (5.4% to 31.6%)
95% CI	(10.7%, 35.7%)	(0%, 14.8%)	(0.2%, 38.5%)	(0%, 45.9%)	(9.7%, 30.9%)	(0%, 11.9%)		

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval

p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline, not adjusted for multiple comparisons.

95% CIs were calculated using the Clopper-Pearson method.

Source: Reviewer's Analysis

Table 9 presents the change in HBV DNA (log10 IU/mL) by visit. Significant decreases in HBV DNA in the TAF group compared with the placebo group were observed from baseline at all measured time points (nominal *p*-value <0.0001 from Week 4 to Week 24).

Table 9: Secondary Efficacy Endpoint Analysis for Change in HBV DNA (log10 IU/mL) by Visit (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

Change in HBV DNA (log_{10} IU/mL)	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)	*p*-value
Week 4							
N	46	23	11	6	57	29	<0.0001
Mean (SD)	-2.93 (0.664)	-0.06 (0.195)	-2.58 (0.860)	0.03 (0.196)	-2.87 (0.711)	-0.04 (0.196)	
Median (min, max)	-2.95 (-4.39, -1.19)	-0.09 (-0.36, 0.35)	-2.55 (-3.71, -0.49)	-0.02 (-0.12, 0.38)	-2.93 (-4.39, -0.49)	-0.09 (-0.36, 0.38)	
Week 8							
N	45	23	10	6	55	29	<0.0001
Mean (SD)	-3.55 (0.977)	-0.05 (0.310)	-3.50 (0.769)	-0.10 (0.168)	-3.54 (0.936)	-0.06 (0.285)	
Median (min, max)	-3.52 (-5.49, -0.96)	-0.04 (-0.77, 0.83)	-3.55 (-4.79, -2.55)	-0.06 (-0.41, 0.08)	-3.52 (-5.49, -0.96)	-0.05 (-0.77, 0.83)	
Week 12							
N	46	22	11	6	57	28	<0.0001
Mean (SD)	-4.01 (1.266)	-0.12 (0.362)	-4.01 (0.950)	-0.04 (0.175)	-4.01 (1.204)	-0.11 (0.330)	
Median (min, max)	-4.19 (-6.30, -0.39)	-0.08 (-1.25, 0.41)	-3.75 (-5.70, -2.89)	0.00 (-0.34, 0.20)	-4.18 (-6.30, -0.39)	-0.06 (-1.25, 0.41)	
Week 16							
N	45	21	12	5	57	26	<0.0001
Mean (SD)	-4.63 (1.344)	-0.17 (0.671)	-4.33 (0.871)	-0.10 (0.188)	-4.56 (1.258)	-0.16 (0.606)	
Median (min, max)	-4.92 (-6.54, -0.60)	-0.02 (-2.95, 0.32)	-4.16 (-6.24, -3.49)	-0.08 (-0.40, 0.07)	-4.74 (-6.54, -0.60)	-0.02 (-2.95, 0.32)	
Week 24							
N	46	22	12	5	58	27	<0.0001
Mean (SD)	-5.04 (1.544)	-0.13 (0.689)	-4.76 (1.466)	0.00 (0.346)	-4.98 (1.520)	-0.10 (0.636)	
Median (min, max)	-5.26 (-6.98, 0.16)	-0.01 (-2.48, 1.06)	-4.87 (-6.59, -1.20)	-0.04 (-0.45, 0.47)	-5.25 (-6.98, 0.16)	-0.02 (-2.48, 1.06)	

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
HBV DNA values below the lower limit of quantification were imputed as 19 IU/mL.
p-values were based on a two-sided Wilcoxon rank sum test, not adjusted for multiple comparisons.
Source: Reviewer's Analysis

Table 10 presents the proportion of participants with baseline abnormal ALT that had normalized ALT by Week 24. Overall, a higher percentage of participants in the TAF group compared with the placebo group achieved ALT normalization.

Table 10: Secondary Efficacy Endpoint Analysis for Proportion of Participants with Normalized ALT at Week 24 (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

Normalized ALT at Week 24	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)	*p*-value
Central Laboratory	28/42 (66.7%)	1/21 (4.8%)	7/10 (70.0%)	0/6 (0%)	35/52 (67.3%)	1/27 (3.7%)	<0.0001
AASLD	20/46 (43.5%)	0/22 (0%)	5/10 (50.0%)	0/6 (0%)	25/56 (44.6%)	0/28 (0%)	<0.0001

ALT = alanine aminotransferase; TAF = tenofovir alafenamide; AASLD = American Association for the Study of Liver Diseases

p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline, not adjusted for multiple comparisons.

Central laboratory normalized ALT was defined as ≤ 34 U/L for females aged 2 or older or males aged 1-9 years old and ≤ 43 U/L for males aged older than 9 years.

AASLD normalized ALT was defined as ≤ 30 U/L for males and females based on the range for pediatric participants.

Source: Reviewer's Analysis

Table 11 presents the proportion of participants with normal ALT at both baseline and Week 24 by central laboratory and AASLD criteria. The proportion of participants with ALT that remained normal was greater for the TAF group compared with the placebo group at Week 24.

Table 11: Secondary Efficacy Endpoint Analysis for Proportion of Participants with Normalized ALT at Baseline and Week 24 (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

Normal ALT	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25mg (N=47)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=59)	Placebo (N=29)	*p*-value
Central Laboratory							
Baseline	5/47 (10.6%)	2/23 (8.7%)	2/12 (16.7%)	0/6 (0%)	7/59 (11.9%)	2/29 (6.9%)	0.4766
Week 24	32/47 (68.1%)	3/23 (13.0%)	9/12 (75.0%)	0/6 (0%)	41/59 (69.5%)	3/29 (10.3%)	<0.0001
AASLD							
Baseline	1/47 (2.1%)	1/23 (4.3%)	2/12 (16.7%)	0/6 (0%)	3/59 (5.1%)	1/29 (3.4%)	0.7338
Week 24	21/47 (44.7%)	1/23 (4.3%)	7/12 (58.3%)	0/6 (0%)	28/59 (47.5%)	1/29 (3.4%)	<0.0001

ALT = alanine aminotransferase; TAF = tenofovir alafenamide; AASLD = American Association for the Study of Liver Diseases

p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline, not adjusted for multiple comparisons.

Central laboratory normalized ALT was defined as ≤ 34 U/L for females aged 2 or older or males aged 1-9 years old and ≤ 43 U/L for males aged older than 9 years.

AASLD normalized ALT was defined as ≤ 30 U/L for males and females based on the range for pediatric participants.

Source: Reviewer's Analysis

Table 12 presents the proportion of participants with HBeAg Loss/Seroconversion by Visit using the serologically evaluable full analysis set for HBeAg Loss/Seroconversion. Overall, the difference of proportion of participants in the TAF and placebo groups that had experienced HBeAg loss/seroconversion was not statistically significant (*p*-value = 0.5242) at Week 24.

Table 12: Secondary Efficacy Endpoint Analysis for Proportion of Participants with HBeAg Loss/Seroconversion by Visit (Missing = Failure) (Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion, Double-Blind Phase) – Study GS-US-320-1092

	Cohort 1		Cohort 2 Group 1		Total		Total TAF 25 mg vs Total Placebo
	TAF 25mg (N=46)	Placebo (N=23)	TAF 25mg (N=12)	Placebo (N=6)	TAF 25mg (N=58)	Placebo (N=29)	*p*-value
Loss							
Week 12	3/46 (6.5%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	4/58 (6.9%)	0/29 (0%)	0.1528
Week 24	3/46 (6.5%)	1/23 (4.3%)	1/12 (8.3%)	0/6 (0%)	4/58 (6.9%)	1/29 (3.4%)	0.5242
Seroconversion							
Week 12	3/46 (6.5%)	0/23 (0%)	1/12 (8.3%)	0/6 (0%)	4/58 (6.9%)	0/29 (0%)	0.1528
Week 24	3/46 (6.5%)	1/23 (4.3%)	1/12 (8.3%)	0/6 (0%)	4/58 (6.9%)	1/29 (3.4%)	0.5242

HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; TAF = tenofovir alafenamide
p-values were based on two-sided Cochran-Mantel-Haenszel tests adjusted for age at baseline, not adjusted for multiple comparisons.
Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion included participants with HBeAg positive and HBeAb negative/missing at baseline.
HBeAg loss was defined as a change from HBeAg positive at baseline to HBeAg negative with baseline HBeAb negative/missing.
HBeAg seroconversion was defined as HBeAg loss and a change from HBeAb negative/missing at baseline to HBeAb positive.
HBeAg 'Borderline' measurements were imputed to 'Positive', and HBeAb 'Borderline' measurements were imputed to 'Negative'.
Source: Reviewer's Analysis

3.3 Evaluation of Safety

Please refer to the clinical review for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg) was not included in the subgroup analysis due to the small sample size (12 participants in the TAF group versus 6 participants in the placebo group).

For Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg), as the majority of participants were Asian (73.9%), and other four race groups were relatively small, subgroup analysis results for race would not be meaningful.

Table 13 presents the subgroup analysis for Cohort 1 by sex. The differences were not significant for the subgroups according to sex.

Table 13: Subgroup Analysis by Sex for Proportion of Participants with HBV DNA < 20 IU/mL At Week 24 (Missing = Failure) (Full Analysis Set, Double-Blind Phase) – Study GS-US-320-1092

HBV DNA <20 IU/mL at Week 24	Cohort 1	
	TAF 25mg (N=47)	Placebo (N=23)
Male		
Proportion	4/27 (14.8%)	0/16 (0%)
95% CI	(4.2%, 33.7%)	(0%, 20.6%)
Female		
Proportion	6/20 (30.0%)	0/7 (0%)
95% CI	(11.9%, 54.3%)	(0%, 41.0%)

HBV = hepatitis B virus; DNA = deoxyribonucleic acid; TAF = tenofovir alafenamide; CI = confidence interval
95% CIs were calculated using the Clopper-Pearson method.
Source: Reviewer's Analysis

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary efficacy endpoint analysis results for Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg) should be used with caution due to the small sample size (12 participants in the TAF group versus 6 participants in the placebo group) and lack of power.

5.2 Collective Evidence

The submitted data at Week 24 provided evidence of superiority of TAF over placebo for the treatment of chronic HBV infection in children and adolescent:

- For the primary efficacy endpoint, overall, the proportion of participants with HBV DNA <20 IU/mL was 18.6% (11 of 59 participants) with TAF versus 0.0% (0 of 29 participants) with placebo (*p*-value = 0.0137) at Week 24; for Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg), the proportion of participants with HBV DNA <20 IU/mL was 21.3% (10 of 47 participants) with TAF versus 0.0% (0 of 23 participants) with placebo at Week 24; for Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg), the proportion of participants with HBV DNA <20 IU/mL was 8.3% (1 of 12 participants) with TAF versus 0.0% (0 of 6 participants) with placebo at Week 24.
- HBV DNA levels progressively declined from baseline to Week 24 in TAF-treated participants and mean (SD) log10 IU/mL decreases were significantly greater

(nominal *p*-value < 0.0001) in participants treated with TAF versus placebo at each time point from Week 4 through Week 24.

- A significantly greater proportion of participants treated with TAF versus placebo achieved ALT normalization at Week 24 when evaluated by both central laboratory and AASLD criteria.
- Rates of HBeAg loss/seroconversion were similar between the TAF and placebo groups, and no participant in either group had HBsAg loss through Week 24.

5.3 Conclusions and Recommendations

The results from the primary endpoint Week 24 analysis of Cohort 1 (adolescent participants aged 12 to < 18 years old weighing ≥ 35kg) and Cohort 2 Group 1 (children aged 6 to < 12 years old weighing ≥ 25 kg) in Study GS-US-320-1092 show that TAF is superior to the placebo for the treatment of chronic HBV infection in the combined cohorts of children and adolescent weighing ≥ 25 kg. However, please note that the Cohort 2 Group 1 results for children aged 6 to < 12 years old weighing ≥ 25 kg should be used with caution due to the small sample size (12 participants in the TAF group versus 6 participants in the placebo group) and lack of power.

5.4 Labeling Recommendations

In Section 14 of the labeling, the Applicant added Section 14.5 to describe the clinical trial in pediatric subjects (b) (4) ages of 12 to less than 18 years (b) (4) This reviewer thinks the current revised labeling updates are appropriate.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YIFAN WANG
10/17/2022 04:32:45 PM

SOMESH CHATTOPADHYAY
10/17/2022 04:33:16 PM