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 Number:	21-356 S-42 SDN 808 eCTD sequence number 0676
Drug Name:	Viread (tenofovir disoproxil fumarate. TDF) 300 mg Tablets once a day
Indication(s):	Treatment of chronic hepatitis B virus infection in adolescent patients ages 12 to less than 18 years weighing 35 kg or greater
Applicant:	Gilead Sciences
Date(s):	Submission stamp date: February 17, 2012 PDUFA goal date: August 17, 2012 Review completion date: July 13, 2012
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
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Medical Division:	Division of Anti-viral Products (DAVP)
Clinical Team:	Clinical Reviewer: Prabha Viswanathan, M.D. CDTL: Linda Lewis, M.D.
Clinical Consult:	Stephen Voss, M.D. Division of Reproductive and Urologic Products (DRUP)
Project Manager:	Katherine Schumann, M.S.

Keywords: Clinical trials

· For subjects with abnormal ALT at baseline, secondary endpoints included ALT normalized; and composite endpoint of HBV DNA < 400 copies/mL and ALT normalized.
· For HBeAg-positive subjects with abnormal ALT at baseline, secondary endpoints included composite endpoint of HBV DNA < 400 copies/mL, ALT normalized and HBeAg loss; and composite endpoint of HBV DNA < 400 copies/mL, ALT normalized, and HBeAg seroconversion.

Plasma for assaying HBV DNA (PCR-based assay) and to measure TDF concentrations was collected with hepatitis B serology at baseline, and Weeks 4, 8, 16, 24, 32, 40, 48, 56, 64 and 72. Dexa scans were performed at baseline and Weeks 24, 48 and 72. Resistance surveillance was done at baseline and, in patients with HBV DNA copies>400, at Weeks 48 and 72.

Use of anti-viral agents with anti-HBV activity was prohibited during the trial. Other medications prohibited are listed on page 50 of the study report.

A Data Monitoring Committee (DMC) reviewed safety data every 24 weeks throughout the trial. No interim analyses of efficacy data were planned or performed.

With a proposed sample size of 50 patients in each arm, the trial was powered at 80% to detect a treatment difference of 30% (assuming a placebo response of 21%) for the primary outcome; a treatment difference of 20% (assuming a placebo response of 2%) for bone metabolism and a treatment difference of 3% (assuming a 0% change for placebo) for percent change from baseline in BMD.

3.1.1.2 Patient Disposition

A total of 149 patients were screened and 106 were randomized to either placebo or TDF (Table 3.2.1.2.1). The reasons why 43 screened patients did not fulfill the entry criteria and therefore were not randomized were not provided in the database or the study report. Patients were randomized at 21 centers in seven countries; the most sites (8) were in Poland where 70% of the patients were randomized. Only 5 patients at 3 centers from the United States were randomized in this study; this low number is not surprising given the low prevalence of this disease in adolescents in the United States.

Five patients (1 TDF and 4 placebo) did not complete 72 weeks on randomized treatment. Three patients (1 TDF and 2 placebo), who dropped out due to investigator decision, did not enter the open label (OL) TDF phase of the study; their average time on trial was 40 weeks. These three patients did not achieve HBsAg loss and therefore were not included in the Week 72 analysis set according to the applicant's algorithm for double-blind efficacy evaluation (DBEE, described on page 85 of the study report). Two placebo patients entered the OL phase but did not complete the DB treatment with each finishing about half of the 72 weeks of randomized treatment; these patients were removed from study due to high ALT in accordance with the protocol.

Table 3.2.1.2.1 Study GS-US-174-0115 Patient Disposition

	TDF	Placebo
Randomized	52	54
Discontinuations	1	4
Investigator decision	1	2
High ALT	0	2
72-week Completers	51 (98%)	50 (93%)
Entered OL follow-up	51	52

The double-blind database was finalized on May 13, 2011. An analysis of OL data is planned when all subjects have completed 144 weeks of treatment (72 weeks of OL treatment). No OL data was included in the application.

3.1.1.3 Baseline Demographics

The treatment groups were balanced for important demographic baseline measures overall and also within age groups (ages12-14 and 14-17). In Table 3.1.1.3.1, descriptive statistics are shown by treatment group. For results by age groups, see page 109 of the study report.

The majority of randomized patients were male (69%) and Caucasian (92%). The mean age of patients was 16 years; the majority of patients were in the 15 to <18 stratum (78%).

Table 3.1.1.3.1 Study GS-US-174-0115 Patient Demographics for All Randomized Patients

	TDF n=52	Placebo n=54
Age (years)		
Mean (SD)[1]	16.1 (1.4)	15.7 (1.5)
Min-Max	12.1-17.99	12.3-17.95
Strata		
12 to <15	10 (19%)	13 (24%)
15 to <18	42 (81%)	41 (76%)
Gender (%)		
Male	73%	65%
Race (%)		
White	94%	91%
Black	2%	0
Asian	2%	2%
Other	2%	7%
Country (n)		
Europe		
Bulgaria	3 (6%)	4 (7%)
France	1 (2%)	1 (2%)
Poland	37 (71%)	37 (69%)
Romania	8 (15%)	6 (9%)
Spain	0	2 (4%)
Turkey	1 (2%)	1 (2%)
North America/US	2 (4%)	3 (6%)
Weight (kg)		
Mean (SD)	61 (12)	58 (11)

The two age strata differed regarding genotype; for patients under 15, about half were genotype D and a little less than half were genotype A, while for the patients over 15, the majority were genotype A (~71%) and about 29% were genotype D.

[1] The means computed by this reviewer differ from the applicant's means reported in the study report Table 8-4 because the applicant computed means using the patient's age measured as an integer (13, 14, 15, etc.) while this reviewer computed means using age measured on a continuous scale (e.g. 12.1) based on the actual age at time of randomization.

Baseline HBV test results (Table 3.1.1.3.2) showed no important treatment group differences and also no differences were seen between groups within each age stratum. The mean HBV DNA at baseline was about 8 $\log_{10}$ copies/mL and ranged from about 5 to 10; note that the inclusion criteria specified that all patients have values of HBV DNA at baseline greater than 5 log. Mean ALT at baseline was 101 U/L with the majority of patients having a value above the upper limit of normal (ULN); about ¼ of the patients had values above 3 times the ULN. The distributions of HBV DNA (Figure 3.1.1.3.2) and ALT (Figure 3.1.1.3.1) are shown in boxplots on the next page. All patients were HBsAg positive as required to enter the trial and about 90% were also HBeAg positive. More than 80% had been previously treated; the entry criteria for the Polish sites required that all patients be previously treated or to have treatment contraindicated; prior treatment with TDF was not allowed.

Table 3.1.1.3.2 Study GS-US-174-0115 Baseline HBV History for All Randomized Patients

	TDF n=52	Placebo n=54
HBV DNA ($\log_{10}$ copies/mL)		
Mean (SD)	8.0 (1.4)	8.2 (1.4)
Median	8.4	8.5
Min-Max	4.9-10.1	4.7-10.1
ALT U/L		
Mean (SD)	101 (108)	101 (90)
% above ULN	67%	78%
% above 2xULN	35%	46%
% above 3xULN	23%	24%
HBsAg Positive	52 (100%)	54 (100%)
HBeAg Positive	48 (92%)	48 (89%)
HBeAg Negative/Anti-HBe Positive	4 (8%)	6 (11%)
Previous HBV treatment experience		
Adefovir	5 (10%)	7 (13%)
Entecavir	0 (0%)	2 (7%)
Lamivudine	31 (60%)	31 (57%)
Interferon	37 (71%)	44 (81%)
None	9 (17%)	7 (13%)
Nucleos(t)ide experience	32 (62%)	33 (61%)
Interferon only experience	11 (21%)	14 (26%)
Risk Factors (some patients had >1 factor)		
Vertical transmission	25%	17%
Blood transfusion	10%	11%
Contact w/infected person	8%	17%
IV drug use	4%	7%
Hospitalization or surg. procedure	19%	31%
Unknown	40%	33%
Years positive for HBV		
Mean (SD)	10.2 (5)	10.8 (5)

Sources include raw dataset PREVHEP, analysis dataset ADSL and Study Report Listing 6.

More than 1/3 of patients had no known risk factor for HBV; the most common risk factor was a previous hospitalization or surgical procedure. About 20% of patients had vertical transmission as a risk factor.

Mean time positive for HBV was 10 years; for patients 12 to <15, the mean time was 8.5 years and for patients >15, the mean was about 11 years.

Figure 3.1.1.3.1 Boxplots of baseline ALT by treatment

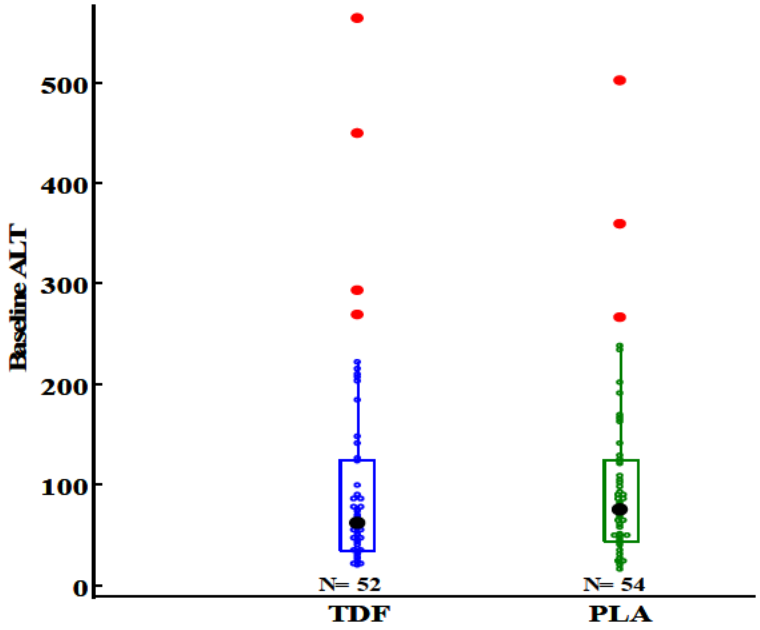
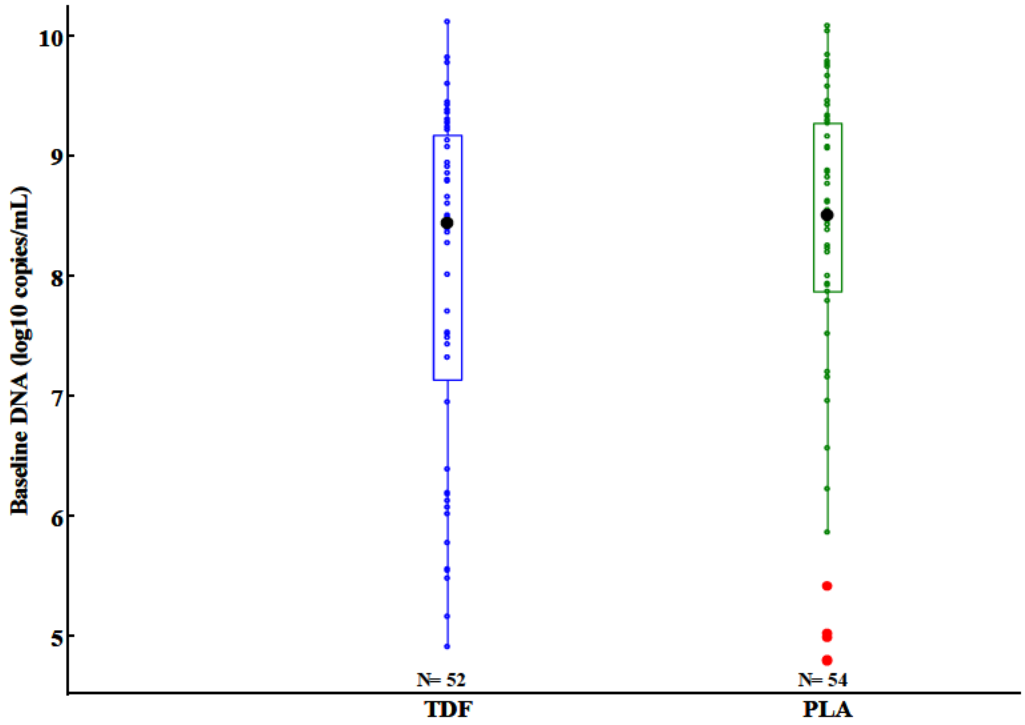


Figure 3.1.1.3.2 Boxplots of baseline HBV DNA (log10 copies/mL) by treatment



In meetings with the FDA anti-viral medical division, medical reviewers questioned whether the TDF effects seen on bone were similar for the HBV adolescent population of Study GS-US-174-0115 reviewed here to the results seen for an HIV adolescent population in Study GS-US-104-0321. The bone data for the HIV population was reviewed by medical reviewer Stephen Voss of DRUP; the review dated 2/10/2010 is available in DARRTS.

This reviewer accessed the submitted bone data for both studies so all the results shown to compare the populations were computed by this reviewer. The same timepoint of 48 weeks was used to summarize the data from both studies because Week 48 was the last double-blind timepoint on the HIV study. For patients missing Week 48 data, the last value prior to Week 48 was used.

The HIV population was 44% male with a mean age of 14 years while the HBV population was predominantly male (70%) and older with a mean age of 16. About 75% of HBV population reported taking vitamins with vitamin D during the trial while only about 10% of the HIV population reported taking vitamin D or a multivitamin according to Dr. Voss's review. Dr. Voss reported mean increases of vitamin D in both HIV treatment groups of about 5 ng/mL at Week 48, which is approximately the same change seen in the HBV population (see Table 3.2.2).

Table 3.2.3 Week 48 LOCF BMD z-score change from baseline results for HBV adolescent patients in Study GS-US-174-0115 and HIV adolescent patients in Study GS-US-104-0321

	TDF Mean (SD) Median	Placebo Mean (SD) Median	Least Squares Mean Difference[1] (95% CI)	p-value[1]
Spine BMD Z-score				
HBV	(n=52)	(n=54)		
Baseline	-0.43 (0.76) -0.50	-0.29 (0.81) -0.18		
Wk 48 Change from baseline	-0.07 (0.26) -0.05	+0.01 (0.32) +0.01	-0.07 (-0.18, +0.04)	0.21
HIV	(n=43)	(n=42)		
Baseline	-1.0 (1.2) -0.90	--0.81 (1.4) -0.86		
Wk 48 Change from baseline	-0.17 (0.59) -0.16	-0.13 (0.36) -0.15	-0.06 (-0.26, +0.15)	0.57
Whole body BMD Z-score				
HBV	(n=52)	(n=54)		
Baseline	-0.22 (1.12) -0.17	-0.26 (0.88) -0..26		
Wk 48 Change from baseline	-0.12 (0.32) -0.11	+0.03 (0.30) -0.01	-0.16 (-0.28, -0.04)	0.01
HIV	(n=43)	(n=42)		
Baseline	-0.85 (1.3) -0.76	-0.58 (1.2) -0.69		
Wk 48 Change from baseline	-0.19 (0.37) -0.20	-0.14 (0.32) -0.14	-0.06 (-0.21, +0.09)	0.41

[1] Least squares mean difference is a baseline-adjusted estimate computed from an analysis of covariance model with baseline as a covariate.

For spine BMD z-scores, the results for the HBV and HIV populations are quite similar with treatment differences of -0.07 and -0.06 respectively ($p>0.20$). The whole body results differ with a statistically significant treatment difference seen for HBV patients but not for HIV patients; however, confidence intervals for the treatment differences overlap suggesting that the results are not inconsistent or contradictory.

After discussions with the FDA medical reviewer for the bone data, Dr. Stephen Voss, this reviewer analyzed the change from baseline and percent change from baseline data for the raw BMD data. Unlike the z-score spine data, the Week 48 and 72 spine BMD data show a significant treatment difference ($p<0.03$, Table 3.2.4).

Based on the change from baseline and percent change from baseline BMD data, both the spine and the whole body BMD data show significantly greater increases in BMD for placebo patients than for TDF-treated patients for HBV patients but not for HIV patients (Table 3.2.4). This data suggests a greater effect of TDF on BMD for HBV adolescents than for HIV adolescents although one should show caution when comparing across studies in that the differences between the results could be due to study differences or population differences unrelated to the differing diseases.

Table 3.2.4 Week 48 LOCF BMD and Week 72 LOCF results for HBV adolescent patients in Study GS-US-174-0115 and Week 48 LOCF BMD results for HIV adolescent patients in Study GS-US-104-0321

	TDF Mean (SD) Median	Placebo Mean (SD) Median	Least Squares Mean Difference[1] (95% CI)	p-value[1]
Spine BMD				
HBV	(n=52)	(n=54)		
Baseline	1.0 (0.16) 1.0	1.0 (0.17) 1.0		
Wk 48 Change from baseline	+0.03 (0.04) +0.03	+0.05 (0.05) +0.05	-0.02 (-0.03, -0.003)	0.02
Wk 48 % change from baseline	+3.6% (4.5) +2.8%	+5.3% (5.6) +4.8%	-1.6% (-3%, -0.1%)	0.03
Wk 72 Change from baseline	+0.05 (0.05) +0.05	+0.07 (0.07) +0.06	-0.02 (-0.04, -0.004)	0.02
Wk 72 % change from baseline	+4.9% (5.4) +4.5%	+7.4% (7.9) +5%	-2.4% (-4.3%, -0.5%)	0.01
HIV	(n=43)	(n=42)		
Baseline	0.87 (0.12) 0.86	0.89 (0.12) 0.88		
Wk 48 Change from baseline	+0.01 (0.05) +0.01	+0.02 (0.05) +0.03	-0.01 (-0.03, +0.01)	0.27
Wk 48 % change from baseline	+1.7% (5.6) +1.5%	+2.6% (5.6) +3.1%	-1.1% (-3.4%, +1.2%)	0.34
Whole body BMD				
HBV	(n=52)	(n=54)		
Baseline	1.1 (0.11) 1.1	1.07 (0.1) 1.05		
Wk 48 Change from baseline	+0.02 (0.03) +0.02	+0.04 (0.03) +0.03	-0.02 (-0.03, -0.007)	0.001
Wk 48 % change from baseline	+1.9% (2.8) +1.6%	+3.7% (3.1) +3.1%	-1.6% (-2.6%, -0.6%)	0.002
Wk 72 Change from baseline	+0.03 (0.04) +0.03	+0.05 (0.04) +0.04	-0.02 (-0.03, -0.007)	0.003
Wk 72 % change from baseline	+3.0% (3.5) +2.7%	+5.0% (4.3) +3.9%	-1.8% (-3%, -0.6%)	0.005
HIV	(n=43)	(n=42)		
Baseline	1.0 (0.01) 1.0	1.0 (0.01) 1.0		
Wk 48 Change from baseline	+0.01 (0.03) +0.01	+0.015 (0.01) +0.01	-0.002 (-0.02, +0.01)	0.78
Wk 48 % change from baseline	+1.3% (2.8) +1.4%	+1.5% (3.5) +1.5%	-0.1% (-1.4%, +1.2%)	0.90

[1] Least squares mean difference is an adjusted estimate computed from an analysis of covariance model with baseline, sex and age as covariates.

As mentioned earlier in this review, six bone biomarkers were measured. The applicant reported that the results for bone biomarkers were similar between the groups. The applicant's Week 72 results (Table 3.2.5) show similar results for the treatment groups comparing the medians numerically. Some measures showed notable differences between the medians and means; for example, for osteocalcin, the treatment difference for the medians is about -1 ng/mL while the difference in the means is about +25 ng/mL This reviewer analyzed the data for two of these endpoints, osteocalcin and PTH, for both the HIV data and HBV data using both a non-parametric test (stratified Wilcoxon rank sum test stratifying on baseline) and an analysis of covariance model with baseline as a covariate; outcome values were correlated with

baseline suggesting the inclusion of baseline in the analyses. The results for the two statistical methods were similar so only the ANCOVA results are shown in the tables.

Table 3.2.5 Study GS-US-174-0115 Applicant's results for bone-specific laboratory results; Medians at baseline and for Week 72 change from baseline

	TDF		Placebo	
	Baseline	Change from Bsl	Baseline	Change from Bsl
N-telopeptide (nmol BCE/L)	34	-5.4	34	-5.6
C-telopeptide (ng/mL)	1.59	-0.22	1.62	-0.32
Serum osteocalcin (ng/mL)	76	-20.5	76	-19.3
Alkaline phosphatase (μg/L)	44	-17	40	-19
PTH (pg/mL)	35	+6	34	-2

For osteocalcin, the Week 48 results for both the HIV and HBV populations showed a statistically difference between TDF and placebo (Table 3.2.6) , Although the HBV patients in both groups showed a decrease in osteocalcin and the HIV TDF patients showed an increase in osteocalcin, the treatments effects (TDF-Placebo) were positive for both populations. So TDF caused less of a decrease (or more of an increase) in osteocalcin than placebo in both populations.

For the HBV population, the magnitude of the treatment effect decreased to about 6 at Week 72 and was not statistically significant (Table 3.2.6).

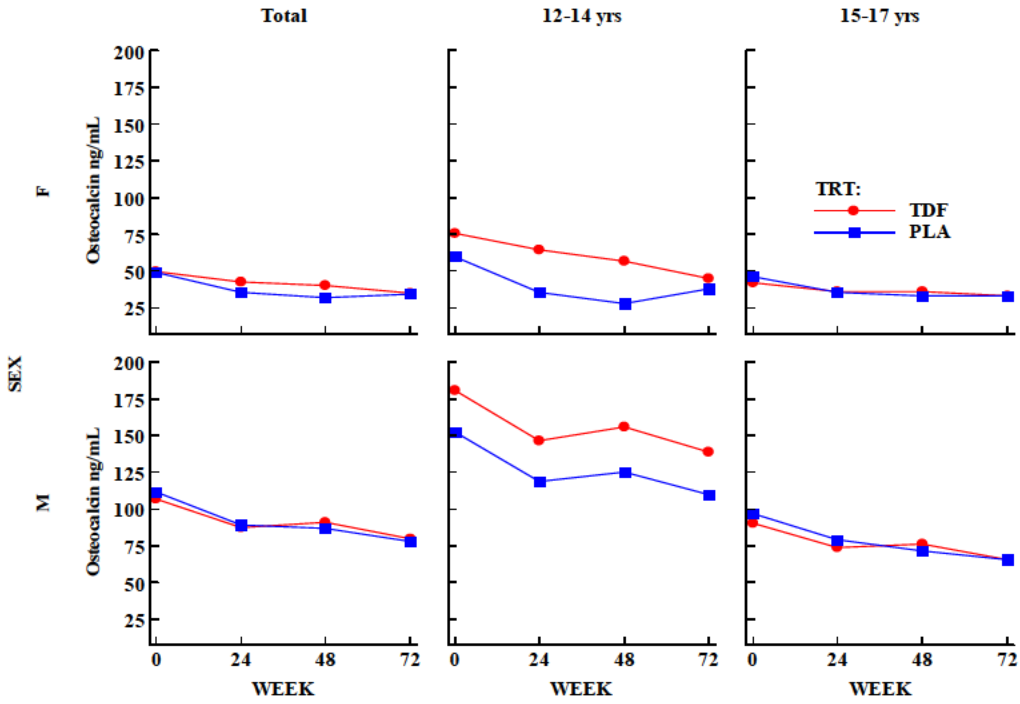
Table 3.2.6 Serum Osteocalcin (ng/mL) for HBV adolescent patients in Study GS-US-174-0115 and HIV adolescent patients in Study GS-US-104-0321

	TDF Mean (SD) Median	Placebo Mean (SD) Median	Least Squares Mean Difference (95% CI)	p-value[1]
HBV	(n=52)	(n=54)		
Baseline	91 (56) 76	89 (59) 89		0.75
Change from baseline				
Week 48 Observed	(n=51)	(n=51)		
	-14 (27) -10	-23 (34) -16	**+11 (+1.0, +20)**	**0.03**
Week 72 Observed	(n=49)	(n=49)		
	-24 (35) -21	-30 (41) -19	+6.9 (-3, +17)	0.18
Week 72 LOCF	(n=52)	(n=54)		
	-24 (35) -21	-29 (39) -18	+6.5 (-3, +16)	0.16
HIV	(n=44)	(n=41)		
Baseline	108 (61) 84.5	92 (58) 78		
Change from baseline				
Week 48 LOCF	+19 (54) +17.5	-8 (41) +2	**+31 (+12, +51)**	**0.002**

[1]ANCOVA model with baseline and stratum as covariates

Figure 3.2.2 on the following page illustrates osteocalcin mean levels overtime by age, sex and treatment groups. These results by sex and age suggest only small insignificant differences between treatment groups.

Figure 3.2.2 Study GS-US-174-0115 Osteocalcin means plotted over time



For parathyroid hormone (PTH), a highly significant treatment effect of +9.3% is seen at Week 48 ($p<0.0003$) for the HBV study but the effect does not persist with the Week 72 LOCF results showing a nonsignificant treatment difference of about +5% ($p=0.12$). The Week 48 results for the HIV population are similar with a borderline significant treatment effect of about 9%.

Table 3.2.6 Study GS-US-174-0115 PTH results for HBV adolescent patients in Study GS-US-174-0115 and HIV adolescent patients in Study GS-US-104-0321

	TDF Mean (SD) Median	Placebo Mean (SD) Median	Least Squares Mean Difference (95% CI)	p-value[1]
HBV	(n=52)	(n=54)		
Baseline	39 (22) 35	40 (22) 34		
Change from baseline				
Week 48 Observed	(n=50)	(n=50)		
	+5.4 (16) +6.8	-4.1 (15) -1.0	**+9.3 (+4.3, +14)**	**0.0003**
Week 72 Observed	(n=51)	(n=50)		
	+1.9 (23) +5.5	-4.1 (22) -1.8	+6.6 (-0.2, +13)	0.056
Week 72 LOCF	(n=52)	(n=54)		
	+1.5 (23) +5.5	-3.5 (21) -1.3	+5.2 (-1.5, 12)	0.12
HIV	(n=44)	(n=41)		
Baseline	44 (27)	50 (21)		
Change from baseline				
Week 48 LOCF	+5.8 (26)	-6.7 (26)	**+8.6 (-1.0, +18)**	**0.07**

[1]ANCOVA model with baseline and stratum as covariates

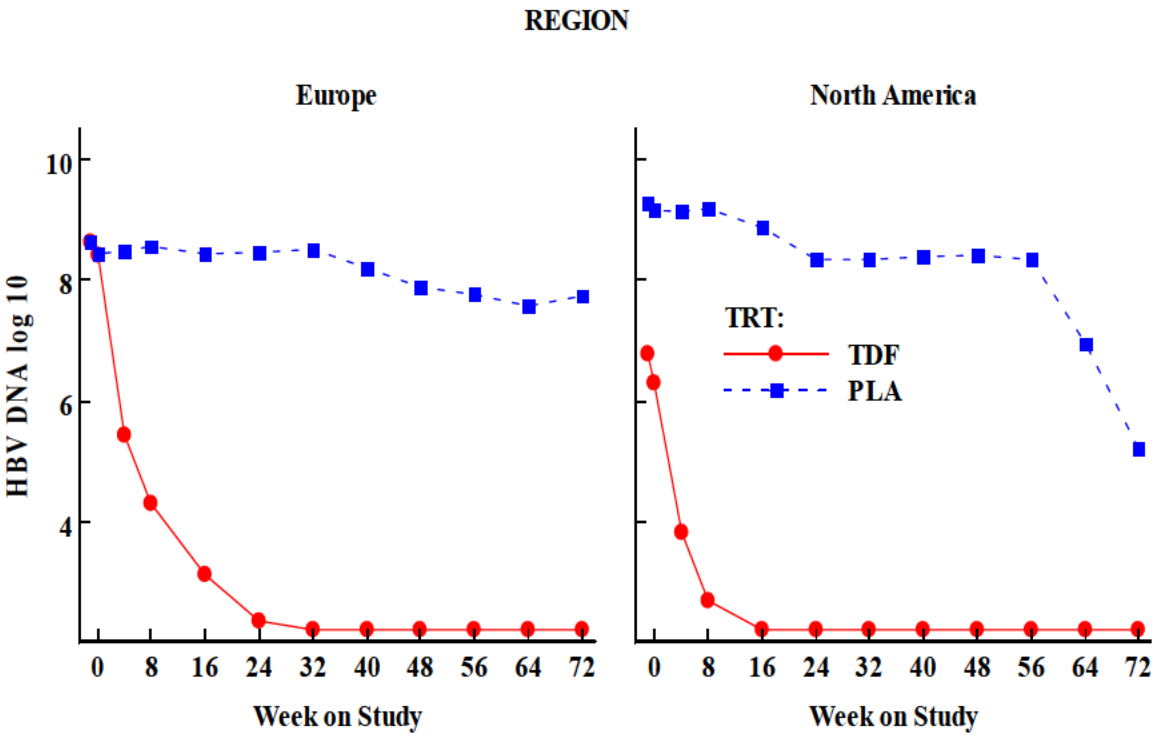
For the HIV population, the relationship between PTH changes and BMD changes was reported in the medical review as not correlated. For this HBV population, whole body BMD change from baseline at Week 72 is also not correlated with changes in PTH with an r^2 of about 0.2. So in both populations, there was no evidence of a relationship between changes in PTH and change in BMD.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The treatment response is not modified by gender, age or geographic region. The similarity of response for HBV DNA for the two geographic regions is illustrated below in Figure 4.1.1. The majority of patients were Caucasians so analyses by race were not appropriate.

Figure 4.1.1 Median HBV DNA (log 10 copies per mL) by study week and region



4.2 Other Special/Subgroup Populations

The applicant presented results for subgroups defined by prior HBV treatment, HBeAg status and baseline ALT (below ULN vs. ULN or higher). Smaller response rates in the TDF group were seen for patients with normal ALT (71%), HBeAG positive (83%) and prior experience with HBV medications (84%). Nevertheless the treatment effect is large for all these subgroups given that no placebo patients responded.

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

With one clinical trial (GS-US-174-0115), the applicant has demonstrated the efficacy of TDF for the treatment of chronic HBV in adolescent children aged 12-17 years. About 89% of TDF-treated patients met the primary endpoint criteria of HBV DNA count less than 400 copies/mL at Week 72 compared to 0% in the placebo group. Changes in bone BMD and bone biochemical markers were consistent with results seen for the HIV adolescent population treated with TDF; however, the unfavorable treatment effects for BMD were generally statistically significant in the HBV population. The impact of these findings on adolescents is not clear with only one traumatic fracture observed in the HBV study.

5.2 Labeling Recommendations

This reviewer has shared comments with the FDA clinical division regarding two paragraphs in the labeling that report results from Study GS-US-174-0115.

In Section 5.6 Decreases in Bone Mineral Density, the following paragraph was proposed by the applicant.

(b) (4)

The following phrase was added to the 4th sentence: compared to +0.07 and +0.06, respectively, in subjects receiving placebo with the estimates added by this reviewer.

In Section 8.4 Pediatric Use, the following paragraph was proposed by the applicant.

Pediatric Patients 12 Years of Age and Older with Chronic Hepatitis B

(b) (4)

This reviewer has the following comments regarding modifying the paragraph above:

- 1st sentence: The majority of the patients were HBeAg positive (92% TDF and 89% PLA) (b) (4).
- 3rd sentence: These results are for patients who had a baseline ALT above the upper limit of normal so the sentence should start with (b) (4)
- 4th sentence: (b) (4)
- All the numbers in this paragraph have been checked by this reviewer and they are correct.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOY D MELE
07/27/2012

GUOXING SOON
07/27/2012