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
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Keywords: Clinical trials

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1 EXECUTIVE SUMMARY

The results of one clinical trial (GS-US-174-0115) were submitted to support the efficacy and safety of Tenofovir disoproxil fumarate (TDF, brand name Viread®) for the treatment of adolescent patients with hepatitis B virus. TDF has been approved for the treatment of HIV-1 infection in adults (2001), for the treatment of HBV infection in adults (2009) and for the treatment of HIV infection in adolescents (2010).

Study GS-US-174-0115 is a Phase 3, 72-week double-blind randomized study designed to compare TDF 300 mg QD to placebo in adolescents 12-17 years old with chronic hepatitis B confirmed by a positive serum HBsAg. A total of 106 patients (52 TDF and 54 placebo) were enrolled at 21 centers in seven countries; the most sites (8) were in Poland (70% of the patients) while only 5 patients were randomized at 3 centers in the United States. The HBV population was predominantly male (~70%) with a mean age of about 16 years. 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. Most patients (~80%) had been previously treated for HBV.

The primary endpoint for the trial is the proportion of patients with an HBV DNA count of less than 400 copies/mL at Week 72. No placebo patients had HBV DNA lower than 400 at Week 72 whereas 89% (46/52) of TDF patients met this criterion ($p<0.0001$). A mean difference (TDF-placebo) in $\log_{10}$ HBV DNA of -4.5 was observed at Week 72 ($p<0.0001$). Of the six TDF patients who were non-responders at Week 72, 3 met the HBV DNA cutoff at an earlier timepoint and the other 3 reached levels close to the cutoff; all six showed increases in TDF accompanied by decreases in TDF concentration.

Only one TDF patient had HBsAg loss and seroconversion at Week 72 compared to none in the placebo group. Twenty-one percent of TDF patients and 15% of placebo patients showed HBeAg loss and seroconversion at Week 72 with the difference not statistically significant..

About 72% of patients had ALT levels above the upper limit of normal at baseline. TDF patients had a significant drop in ALT compared to placebo patients with the effect primarily seen by Week 8 in TDF patients with abnormal baseline ALT. For patients with abnormal baseline ALT, 74% of TDF patients versus 33% of placebo patients were normalized ($p<0.0001$).

The primary endpoint for safety was cumulative incidence of at least a 6% decrease from study baseline in spine BMD (g/cm^2, DEXA scan) through Week 72. Since no patients has a 6% decrease in spine BMD, bone safety was assessed based on several other measures including change or percent change in BMD at the spine and for the whole body, z-scores for spine and whole body and several biochemical bone markers. The applicant concluded that the changes seen in z-scores for the spine BMD and whole body BMD were "not considered to be clinically relevant" (pages 194 and 199 of the study report). Non-significant changes in z-scores at the spine were seen (treatment difference of -0.10 SD, $p=0.18$) while significant differences were seen for the whole body (treatment difference of -0.19 SD, $p=0.01$). These z-score treatment differences were consistent with the changes seen in the adolescent HIV population where a treatment difference of -0.06 was seen for both spine and whole body ($p>0.4$) at Week 48. Likewise treatment differences for changes in osteocalcin and PTH levels were similar for the two adolescent populations with significant increases for TDF compared to placebo observed for osteocalcin and for PTH at Week 48.

In conclusion, TDF was highly effective in reducing HBV DNA levels for 72 weeks compared to placebo. An impact on bone was observed with decreases in BMD seen at the spine and for the whole body.

2 INTRODUCTION

Tenofovir disoproxil fumarate (TDF, brand name Viread®) was first approved for the treatment of HIV-1 infection in adults on October 26, 2001. In August, 2008, TDF was approved for the treatment of chronic hepatitis B (CHB) in nucleoside treatment-naïve adult patients with labeling based on Week 96 results. Subsequent to that approval, in October 2009, supplemental NDAs updated the labeling with results at Week 144 and Week 192 from the originally submitted studies. Tenofovir was approved March 24, 2010 for the treatment of HIV infection in adolescents 12 to less than 18 years primarily based on pharmacokinetic data.

For the present submission, an indication for adolescent patients with hepatitis B virus is being sought. According to the applicant's cover letter, the results from one submitted study, GS-US-174-115, are intended to fulfill the postmarketing study commitments for this age group under PREA and also are intended to fulfill the relevant terms of an FDA Written Request for Pediatric Studies (dated October 19, 2010) for patients 12 to < 18 years of age. This submission is considered a partial response to the Viread HBV written request and is granted a priority review under the Best Pharmaceuticals for Children Act..

2.1 Overview

The results of one Phase 3 clinical trial (GS-US-174-0115) were submitted to support an indication for treatment of HBV in adolescents (Table 2.1.1).

Table 2.1.1 Clinical Trial

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
GS-US-174-0115	Phase 3 Randomized, double-blind, placebo-controlled	72 weeks DB	120 weeks OL of TDF	TDF 300 mg QD n=52 PBO QD n=54	Adolescents (aged 12–17 years) with compensated CHB

A trial (GS-US-174-0144) in patients 2 to <12 years is planned and had not begun recruitment by the time of this submission. The applicant has several ongoing trials in adults with chronic hepatitis B.

2.2 Data Sources and Quality

The submission (sequence 676) is accessible in Global Submit at the following link:
\\CDSESUB1\EVSPROD\NDA021356\021356.enx

The study report for Study GS-US-174-0115 can be directly accessed at:
\\CDSESUB1\EVSPROD\NDA021356\\0676\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hbv\5351-stud-rep-contr\gs-us-174-0115-72wk\report-body.pdf

The define file for the analysis datasets can be directly accessed at:
\\CDSESUB1\EVSPROD\NDA021356\\0676\m5\datasets\gs-us-174-0115-72wk\analysis\datasets\define.pdf

The statistical analysis plan for Study GS-US-174-0115 can be accessed at:
\\CDSESUB1\EVSPROD\NDA021356\\0676\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hbv\5351-stud-rep-contr\gs-us-174-0115-72wk\statistical-methods.pdf

This reviewer also accessed data from a Viread adolescent HIV study (GS-US-104-0321) available at the following link:
\\CDSESUB1\EVSPROD\NDA021356\0569

The data was sufficiently organized and defined to allow review and analyses without requests to the applicant. Analysis datasets used standardized naming conventions but the format was not standardized according to CDISC ADaM format. Note that ADaM formatting is not required for submissions to CDER but is recommended. Nevertheless both the raw and analysis datasets were adequate for review.

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3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study GS-US-174-115 (conducted 12/2008 to 3/2011)

3.1.1.1 Design

Study GS-US-174-0115 is a double-blind, randomized, parallel, placebo-controlled, Phase 3 trial. Adolescent patients with hepatitis B were randomized to tenofovir or placebo and treated for 72 weeks. Randomization was stratified by age (12–14 or 15–17) and geographical location of study site (North America or Europe). After 72 weeks of treatment, all patients were given the option to continue on open-label tenofovir for up to 192 weeks (4 years). Patients who stopped treatment were followed for an additional 24 weeks or until starting active treatment. The focus for this review is the 72 weeks of double-blind treatment.

The criteria for selecting patients for enrollment included the following:

- Male or female aged 12 to 17 years
- Documented chronic HBV infection, defined as positive serum HBsAg for 6 months or longer. For the Polish sites, patients were also required to have a history of prior HBV treatment (e.g. previously treated with interferon or other drug intended to treat this indication) or a contraindication for treatment of HBV with existing drugs for this indication
- HBeAg-positive or HBeAg-negative (a maximum of 50% of subjects may have been HBeAg-negative)
- HBV DNA $\geq 10^5$ copies/mL (PCR method)
- ALT $\geq 2 \times$ ULN at screening, OR any history of ALT $\geq 2 \times$ ULN over the past $\leq$ 24 months

Additional inclusion and exclusion criteria are listed on pages 44-46 of the study report.

The primary endpoint for the trial is the number of patients with an HBV DNA count of less than 400 copies/mL at Week 72. The original protocol defined a responder for the primary endpoint as a patient having HBV DNA count of less than 400 copies/mL and also a normal ALT at Week 72. The normalized ALT part of the endpoint was dropped because patients could qualify for the trial based on ALT values recorded prior to screening; therefore, some subjects could have normal ALT values at baseline making the combination endpoint not evaluable. FDA agreed to the change in endpoint that was recorded in Amendment 2. Note that the primary endpoint used for adults in previous trials of HBV was HBV DNA levels < 400 copies/mL and histologic improvement indicated by at least a 2-point reduction in Knodell necroinflammatory score without worsening in Knodell fibrosis score at Week 48.

Secondary endpoints, measured at Weeks 48 and 72, included measures of ALT, HBV serology and composite endpoints including the following defined for specific groups of patients:

- For all subjects, a composite endpoint of HBV DNA < 400 copies/mL and ALT normal; HBV DNA < 169 copies/mL; HBsAg loss and seroconversion.
- For HBeAg-positive subjects, secondary endpoints included normalized ALT; HBeAg loss and seroconversion; composite endpoint of HBV DNA < 400 copies/mL, ALT normal and HBeAg loss; and composite endpoint of HBV DNA < 400 copies/mL, ALT normal, and HBeAg seroconversion.

· 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

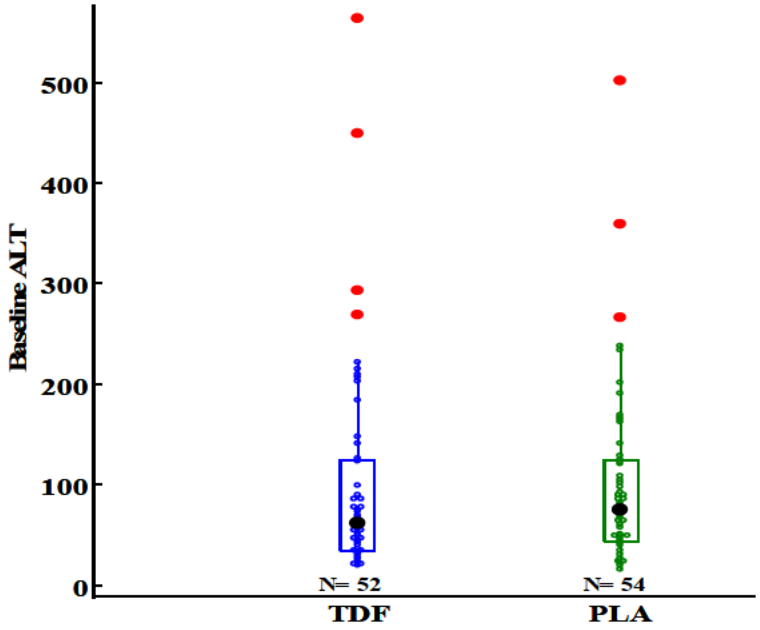
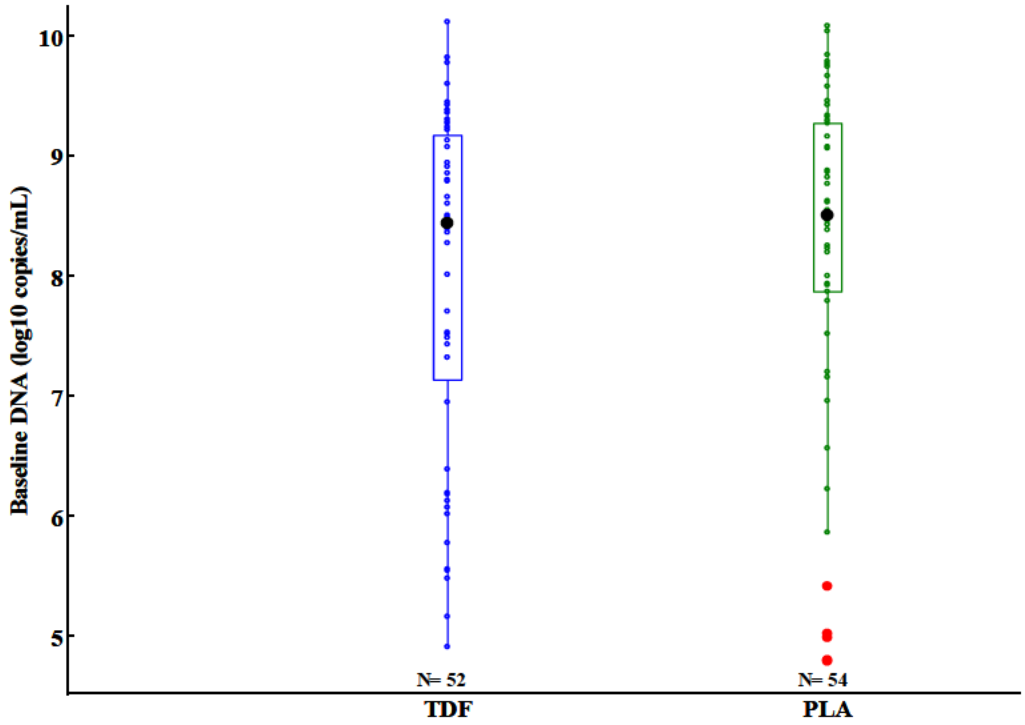


Figure 3.1.1.3.2 Boxplots of baseline HBV DNA (log10 copies/mL) by treatment



The age groups differed in their baseline BMD levels with older patients having higher BMD values (Table 3.1.1.3.3 and Figures 3.1.1.3.3 and 3.1.1.3.4) . Overall, with strata combined, the treatment groups were comparable for baseline BMDs and Z-scores; however, a significant treatment difference in baseline whole body and spine z-scores were seen in the lower age stratum. The latter suggests that baseline values should be considered in the analysis of the BMD data, particularly if baseline is correlated with outcome.

Table 3.1.1.3.3 Study GS-US-174-0115 Baseline BMD baseline values by age strata and treatment

	12 to <15		**15 to <18**	
	TDF (n=10)	Placebo (n=12)	TDF (n=42)	Placebo (n=41)
BMD Mean (SD)				
Spine				
g/cm^2	0.81 (0.08)*	0.89 (0.13)	1.05 (0.14)	1.04 (0.15)
z-score	-0.78 (0.53)**	-0.05 (0.78)	-0.34 (0.79)	-0.35 (0.82)
Whole body				
g/cm^2	0.95 (0.04)	1.0 (0.08)	1.1 (0.1)	1.09 (0.09)
z-score	-0.66 (0.64)*	+0.04 (0.89)	-0.10 (1.2)	-0.35 (0.86)

*0.05<p<0.1 compared to placebo, Wilcoxon test ** p<0.05 compared to placebo, Wilcoxon test

Figure 3.1.1.3.3 Baseline whole body BMD by age strata and by treatment

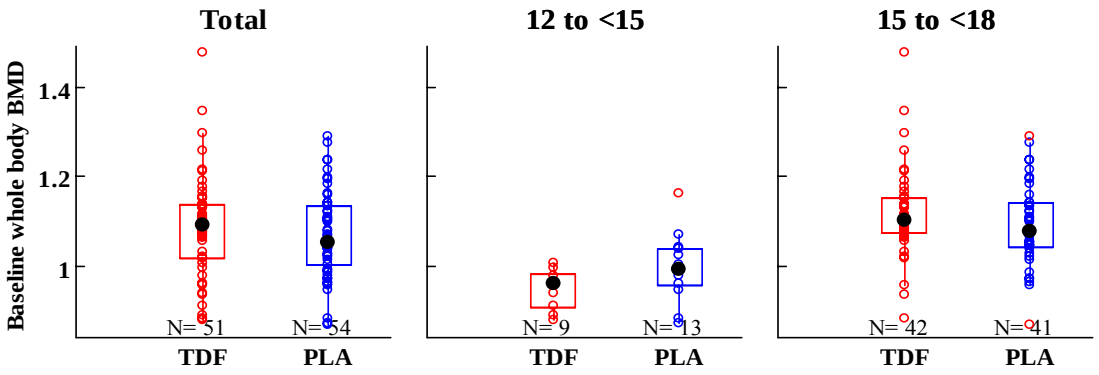
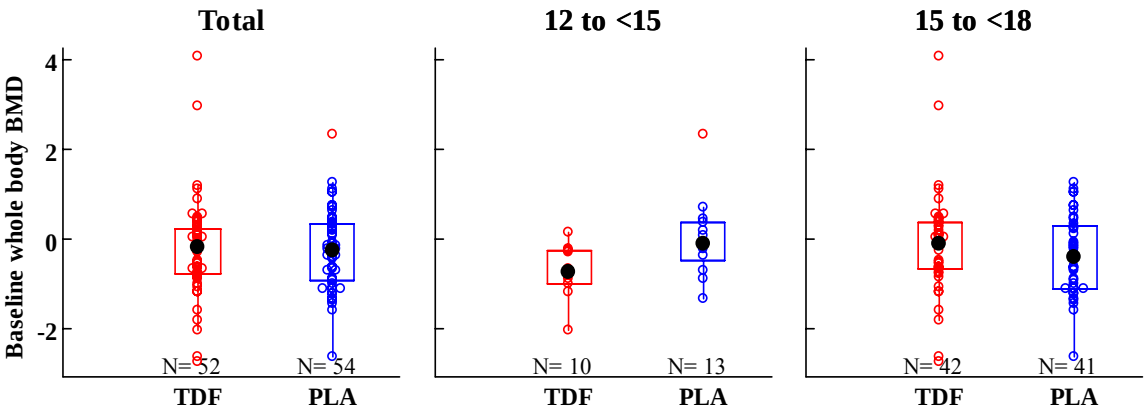


Figure 3.1.1.3.4 Baseline whole body BMD Z score by age strata and by treatment



3.1.1.4 Statistical Methodologies

All subjects randomized who received study drug were included in the analysis population for the applicant and for this reviewer. Patients who did not complete 72 weeks were considered failures for the primary endpoint according to the protocol (page 72). According to the SAP, "data will not be imputed for visits or time points with missing data" except for patients experiencing an HBsAg loss who continue into a treatment free follow-up. For the latter patients, data collected in the treatment free follow-up period would be used and also missing visit data would be imputed with the last value recorded before the visit. There were two patients who experienced HbsAg loss during the trial however neither discontinued study early nor entered the treatment-free follow-up; both entered the open-label phase. Five patients (4 placebos and 1 TDF) discontinued treatment early and had no observation at Week 72. For all 5 patients, the last HBV DNA value recorded was greater than 400 so if one was to impute based on the last value, the results would be the same as counting all discontinued patients as failures.

Study windows were defined for each visit and are listed on page 21 of the SAP. For Week 72, the nominal visit day was Day 504 and the window went from Day 477 to Day 532. When multiple values occurred within a visit window, a single value was chosen based on the following:

- For serology, the last pair (antigen and antibody) of results within the window will be used
- For ALT, the highest value will be used
- For HBV DNA, the closest value to the nominal day will be used. If two dates satisfy this criterion, the latest value will be used. If two values occur on the same day, the second value will be used.
- For other parameters, the value on the day closest to the nominal day will be used.

This reviewer checked which HBV DNA values were chosen for each visit window using the complete HBV DNA data (raw dataset).

The lower limit of quantification for the HBV DNA assay (Roche COBAS Taqman 48 assay) is 169 copies/mL; the value recorded in the database for those levels measured below the lower limit was 168.

Baseline day was defined as the first study day (i.e. first day of randomized treatment). If no value was recorded on that day for a parameter, then the last recorded value before the baseline day was used.

The primary endpoint was analyzed by the applicant using a Cochran-Mantel-Haenszel (CMH) test controlling for age stratum (12 to <15 or 15-<18). Categorical secondary endpoints were also analyzed using the CMH test. Secondary continuous efficacy endpoints were compared with a stratified Wilcoxon test.

Subgroup analyses were planned by the applicant for the primary endpoint as well as for some secondary endpoints.

No adjustments for multiplicity were planned of the efficacy data because only one treatment comparison was considered primary for efficacy and no interim analyses were planned.

Percent change in spine BMD was the primary safety outcome. For analysis, according to the SAP, patients with at least a 6% decrease in spine BMD were considered failures and the proportions satisfying this criterion were to be compared. Also, the SAP stated that a time to event analysis would be performed for this endpoint. However, no patients satisfied this criterion so this analysis was not performed; percent

changes in spine BMD ranged from -4% to +19% for the two treatment groups. The applicant compared treatment groups for percent changes and z-score changes using a nonparametric test stratifying on age group (stratified Wilcoxon test). This reviewer focused on z scores and performed analyses of covariance with baseline as a covariate. Z scores for BMD are scores standardized for both age and sex and would thereby be a preferred outcome for this adolescent population. There was no evidence of departures from normality for the z-score data and so a parametric test is appropriate.

3.1.1.5 Efficacy Results

The primary efficacy endpoint for this study is the proportion of patients with HBV DNA< 400 copies/mL at Week 72. Patients missing a Week 72 value were counted as failures for this endpoint. There were only 5 patients (1 TDF, 4 placebos) with missing values for HBV DNA at Week 72; none of these 5 patients had a recorded HBV DNA value less than 400. The cutoff of 400 was originally chosen because it is the lower limit of some assays used to measure HBV DNA. For the assay for this study, the lower limit was 169 so some patients had values as low as 169. Results for both the 400 cutoff and the 169 cutoff are provided below. Also results for a third cutoff of 1,000 are provided as a test of the robustness of the results using a value considered to be low but not at the cutoff of an assay.

Table 3.1.1.5.1 Study GS-US-174-0115 Week 72 primary efficacy results

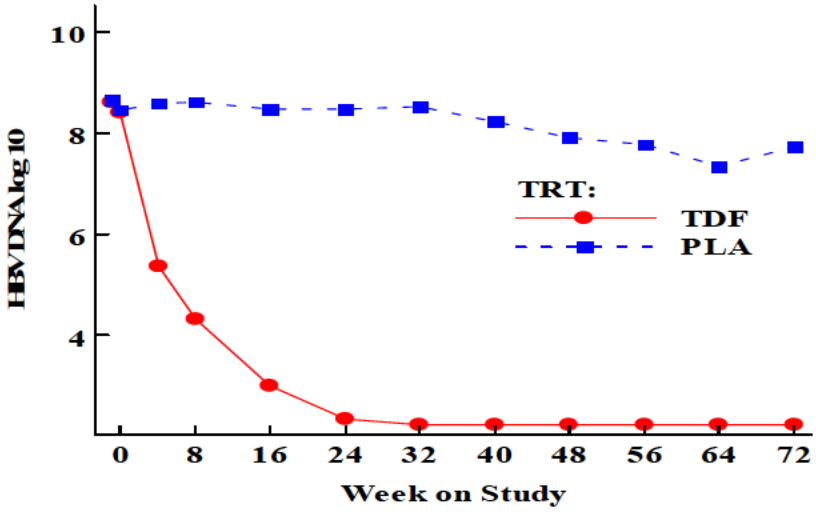
	TDF (n=52)	**Placebo** (n=54)	**Difference (95% CI)**	**p-value[1]**
HBV DNA copies/mL				
%< 400	46 (88.5%)	0 (0%)	88.5% (80%, 97%)	<0.0001
%< 1000	46 (88.5%)	0 (0%)	88.5% (80%, 97%)	<0.0001
%≤ 169	44 (85%)	0 (0%)	85% (75%, 94%)	<0.0001
log_{10} HBV DNA	**Mean (SD)**	**Mean (SD)**		
Baseline	8.0 (1.4)	8.2 (1.4)		
Week 72	2.6 (1.5)	7.2 (1.8)		
Change from baseline	-5.4 (2.0)	-0.92 (1.9)	-4.5 (-5.2, -3.7)	<0.0001

[1]CMH stratifying on age strata for responder analyses. Analysis of covariance stratifying on age strata for change from baseline analysis

No placebo patients were responders regardless of the cutoff level of HBV DNA used so all comparisons to TDF were highly significant (Table 3.1.1.3.3). The TDF response for this population of adolescents is consistent with what was seen for HBV adults where more than 90% of TDF patients had an HBV DNA less than 400.

Median log_{10} HBV DNA plotted over the duration of the trial (Figure 3.1.1.5.1 on the following page) illustrates that the response to TDF occurs within the first month of treatment and is complete by about 6 months for most patients.

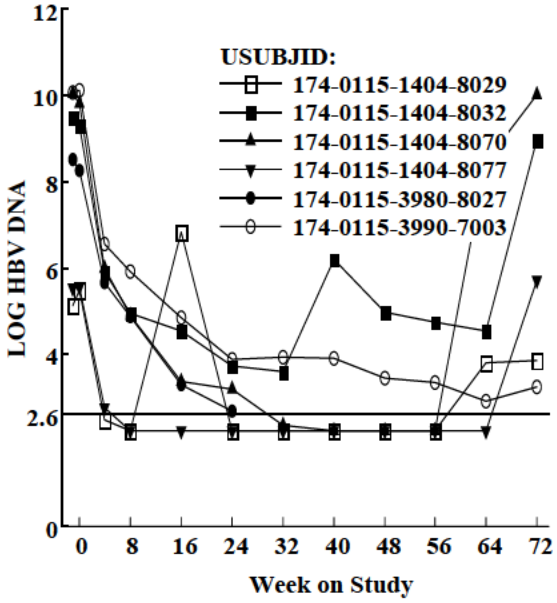
Figure 3.1.1.5.1 Median HBV DNA (log 10 copies per mL) by study week



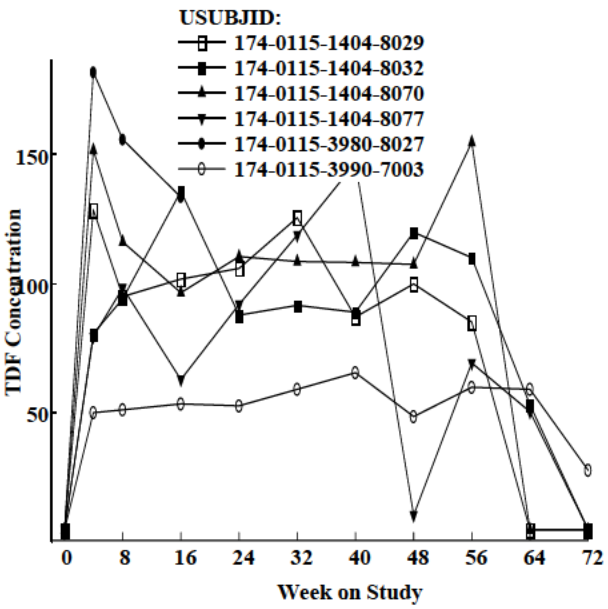
Six TDF patients were non-responders based on the week 72 results for HBV DNA. The log HBV DNA results and TDF concentrations of these six patients are shown below (Figure 3.1.1.5.2). Three patients respond early and then with a drop in TDF concentration show a consequent rise in log HBV DNA. The other three patients show drops in HBV DNA but do not reach the responder cutoff of 400. These results support the strong results seen overall.

Figure 3.1.1.5.2 Results for TDF non-responders

Log HBV DNA



TDF Concentration



Secondary endpoints included counts of patients with antigen loss with or without seroconversion for HBsAg and HBeAg. All patients with HBsAg loss or HBeAg loss also had evidence of seroconversion.

All patients were HBsAg positive at baseline as required by the entry criteria; at Week 72, only 1 TDF patient had HBsAg loss and seroconversion (Table 3.1.1.5.1). A second TDF patient had HBsAg loss at Week 32 but it was not sustained and no seroconversion was observed.

The majority of patients (48 in each group) were HBeAg positive at baseline. Although more TDF patients (10) than placebo patients (7) experienced loss and seroconversion, the difference was not statistically significantly different. The results for the two age strata were reversed with a -12% treatment difference for the younger stratum and a +12% difference for the older stratum, however, the confidence intervals for these treatment differences are wide and the treatment by stratum interaction is not significant (p=0.21).

Another secondary endpoint named in the protocol was the composite endpoint of HBeAg loss and serconversion with HBV DNA<400 copies. Of course given the high response for the primary endpoint seen for the TDF group and the lack of any response seen for the placebo group, the statistical significance seen for the treatment difference of this composite is totally predictable (15% versus 0%, p<0.01).

Table 3.1.1.5.2 Study GS-US-174-0115 HBV serology results at Week 72

	TDF (n=52)	Placebo (n=54)	Treatment Difference (95% CI)	p-value[1]
Baseline				
HBsAg Positive	52 (100%)	54 (100%)		
HBeAg Positive	48 (92%)	48 (89%)	NA	NS
HBeAg Negative/Anti-HBe Positive	4 (8%)	6 (11%)		
Week 72				
HBsAg Loss & Seroconversion	1 (2%)	0 (0%)		NS
Week 72				
HBeAg Loss & Seroconversion				
All patients	10/48 (21%)	7/48 (15%)		NS
12-14 year olds	11%	23%	-12% (-43%, +19%)	*Interaction*
15-17 year olds	23%	11%	+12% (-5%, +28%)	*P=0.21*
Week 72				
HBeAg Loss & Seroconversion & HBV DNA<400	15%	0%		p<0.01

[1]CMH stratifying on age strata

Normalized ALT was considered an important efficacy endpoint and was named as a component of several composite endpoints named by the applicant. Note that all these composite endpoints looked at ALT as dichotomous (normal versus not normal) and a component with the primary endpoint. Given the highly significant results for the primary endpoint with no placebo patients meeting the HBV DNA cutoff value of 400, there is not much added information about the drug by considering composites that include the primary endpoint. Therefore this reviewer looked at ALT as both a continuous measure and as a dichotomous outcome (see Table 3.1.1.5.3 on the following page).

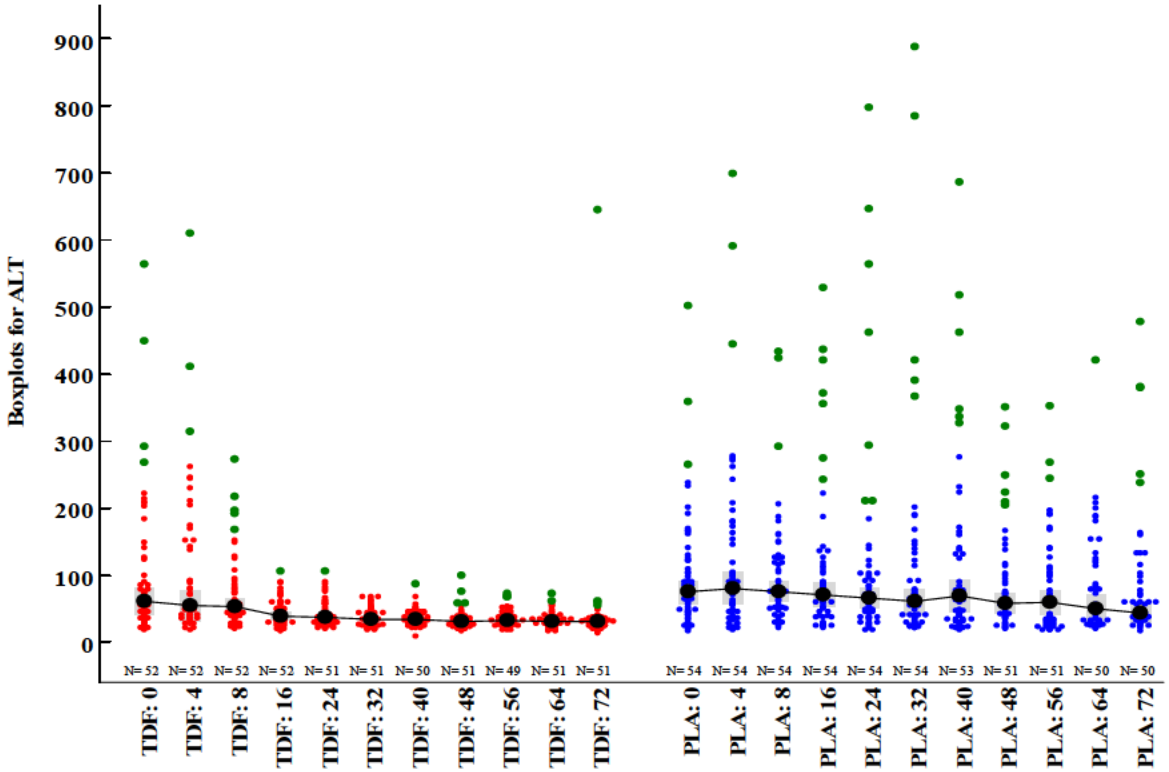
For patients with abnormal ALT's at baseline, significantly more TDF patients (74%) had normal ALT at Week 72 than placebo patients (33%). Also for all patients, a significantly larger drop in ALT is seen for TDF patients than placebo patients (Table 3.1.1.5.3).

Table 3.1.1.5.3 Study GS-US-174-0115 Week 72 ALT results

	TDF (n=52)	Placebo (n=54)	
Normalized ALT			
By baseline ALT Normal ALT Abnormal ALT	 15/17 (88%) 26/35 (74%)	 8/12 (67%) 14/42 (33%)	 p<0.0001
ALT U/L			
	Mean (SD) Median	Mean (SD) Median	
Baseline Change from baseline	101 (108) 61.5 -57 (120) -26	101 (90) 75 +15 (207) -4	 p<0.009

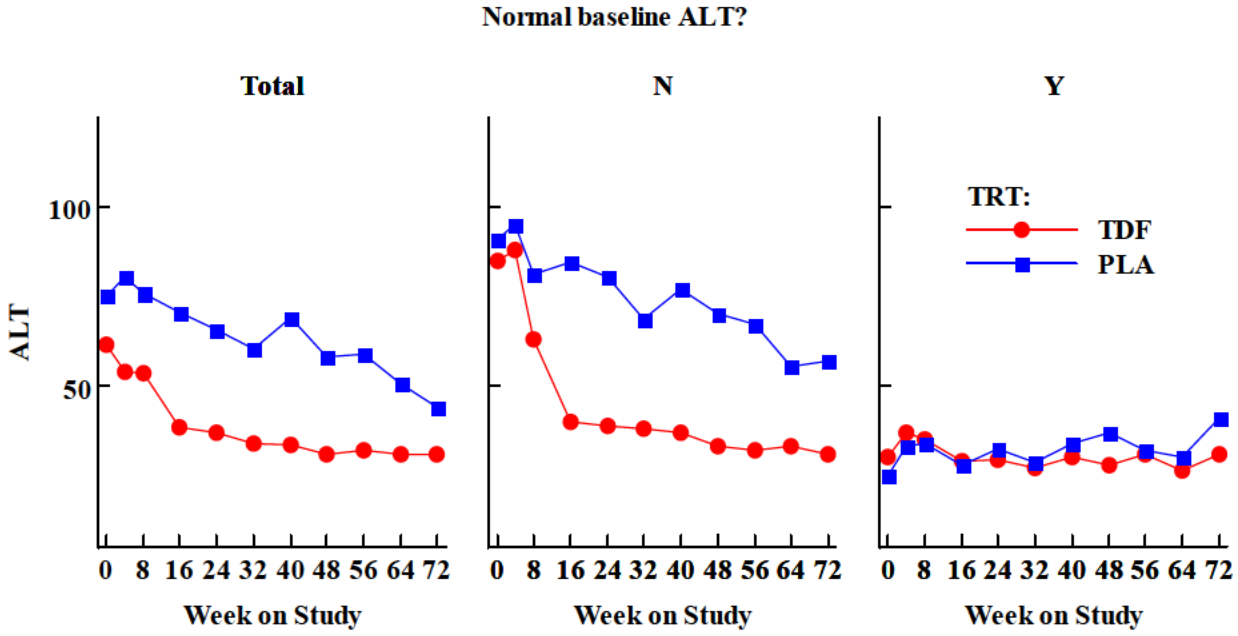
Boxplots of ALT (Figure 3.1.1.5.3) illustrate the distribution of the data by study week with outliers noted in green. In addition to the ALT decreasing overtime in the TDF group, there are clearly fewer patients with large values out of the normal range compared to the placebo group.

Figure 3.1.1.5.3 Boxplots of ALT levels (U/L) by treatment group and week on study



The similarity between the groups of ALT levels for patients with normal baseline ALT is illustrated below. For patients with abnormal baseline ALT values, the effect of TDF is clear with a large drop in ALT at about Week 8 (Figure 3.1.1.5.4).

Figure 3.1.1.5.4 Median ALT (U/L) by week on study and baseline ALT



3.2 Evaluation of Safety

The primary endpoint for safety was cumulative incidence of at least a 6% decrease from study baseline in spine BMD (g/cm^2, DEXA scan) through Week 72. In addition to measuring spine BMD as an endpoint, whole body BMD and serum bone biochemical markers were endpoints as well. Secondary safety endpoints included percent change from baseline for spine and whole body BMD, z-scores for spine and whole body and change in z-scores for spine and whole body.

The following bone biochemical markers were assessed:

- N-telopeptide (nmol BCE/L)
- C-telopeptide (ng/mL)
- Serum osteocalcin (ng/mL)
- Bone-specific alkaline phosphatase (µg/L)
- Serum parathyroid hormone (PTH, [pg/mL])
- Vitamin D (25-hydroxy, [ng/mL])

Only 7 patients had DEXA scans that were considered of poor quality. For six of the 7 patients, there was another scan that provided results for the visit with the poor quality scan and so all six were included in the analyses. One patient (174-0115-1404-7011) was missing a Week 72 result for spine BMD due to a poor quality scan. The spine BMD for the poor quality scan for this patient had values very close to the acceptable scans. This same patient also had no baseline spine BMD data in the ADSL file (baseline demographic analysis file) but has baseline data in the spine analysis dataset. This available data was used to include this patient in this reviewer's analysis.

No patients in either treatment group had a 6% or greater decrease in lumbar spine decline so no analyses could be done of this safety endpoint.

The applicant reported that both groups showed increases in BMD but significantly larger increases were seen in the placebo group (Table 3.2.1) at the spine and for the whole body with a larger treatment difference seen for the whole body.

Table 3.2.1 Study GS-US-174-0115 Applicant's lumbar spine and whole body BMD results

	TDF (n=52) Mean (SD)	Placebo (n=54) Mean (SD)	p-value[1]
Spine BMD			
Baseline	1.00 (0.16)	1.01 (0.16)	
Week 48 % change	+3.5% (4.5)	+5.6% (5.7)	0.046
Week 72 % change	+5.0% (5.5)	+8.1% (8.0)	0.053
Whole Body BMD			
Baseline	1.09 (0.12)	1.07 (0.10)	
Week 48 % change	+2.1% (2.8)	+3.9% (3.2)	<0.001
Week 72 % change	+2.8% (3.5)	+5.4% (4.3)	0.013

[1]Applicant's results of stratified Wilcoxon rank sum test with age groups as stratifier

The applicant provided BMD z-score results but did not analyze these results and simply stated that the spine BMD z-score treatment differences and the whole body BMD z-score treatment differences were "not considered to be clinically relevant" (pages 194 and 199 of the study report).

This reviewer focused primarily on the BMD z-scores for the spine and the whole body because age and gender are important factors in interpreting BMD results and z-scores are computed based on matching each patient to a reference group based on age and gender. This choice is predicated on the assumption that an appropriate reference group was used. The FDA medical reviewer, Dr. Voss, was also interested in the raw BMD values and so that data is shown later in Table 3.2.4.

There was only one small discrepancy between the results presented here (Table 3.2.2) and the study report results with the TDF sample size for whole body data at Week 72 at 45 here while the applicant reported 44 patients. One TDF patient was missing baseline data in the analysis file of whole body BMD but had three baseline values in the raw dataset which this reviewer averaged to obtain a baseline value.

Table 3.2.2 Study GS-US-174-0115 Lumbar Spine and whole body BMD z-score results and Vitamin D results

	TDF (n=52) Mean (SD) Median	Placebo (n=54) Mean (SD) Median	Least Squares Mean Difference (95% CI)	p-value[1]
Spine BMD Z-score				
Baseline	-0.43 (0.76) -0.50	-0.29 (0.81) -0.18		>0.4
Week 48 Observed	(n=51)	(n=50)		
Z-score	-0.51 (0.80) -0.44	-0.30 (0.90) -0.20		
Change from baseline	-0.08 (0.25) -0.05	+0.01 (0.33) +0.01	-0.08 (-0.20, +0.03)	0.16
Week 72	(n=47)	(n=48)		
Observed				
Z-score	-0.43 (0.79) -0.43	-0.22 (0.86) -0.07		
Change from baseline	-0.05 (0.31) -0.05	+0.07 (0.38) +0.07	-0.12 (-0.26, +0.02)	0.09
LOCF	(n=52)	(n=54)		
Z-score	-0.48 (0.84) -0.43	-0.25 (0.89) -0.18		
Change from baseline	-0.06 (0.32) -0.05	+0.04 (0.38) +0.02	-0.10 (-0.23, +0.04)	0.16
% w/ > 1 SD decrease	0%	0%		
%<Baseline z-score	58%	44%		0.18
Whole body BMD Z-score				
Baseline	-0.22 (1.12) -0.17	-0.26 (0.88) -0..26		>0.6
Week 48 Observed	(n=49)	(n=49)		
Z-score	-0.43 (0.97) -0.34	-0.24 (0.93) -0.25		
Change from baseline	-0.11 (0.31) -0.10	+0.03 (0.32) -0.01	-0.14 (-0.27, -0.02)	0.03
Week 72	(n=45)	(n=49)		
Observed				
Z-score	-0.29 (1.01) -0.40	-0.21 (0.92) -0.17		
Change from baseline	-0.14 (0.38) -0.18	+0.06 (0.36) 0.00	-0.19 (-0.34, -0.04)	0.01
LOCF	(n=52)	(n=54)		
Z-score	-0.36 (1.08) -0.39	-0.21 (0.93) -0.21		
Change from baseline	-0.14 (0.39) -0.19	+0.05 (0.35) -0.01	-0.19 (-0.33, -0.05)	0.01
% w/ > 1 SD decrease	0%	0%		
% <Baseline z-score	62%	50%		0.25
Vitamin D (25-hydroxy)				
Baseline	20 (7) 20	20 (8) 19	Not Computed	
Change from baseline				
Week 72 Observed	+6 (10) +5	+5 (10) +4		0.53

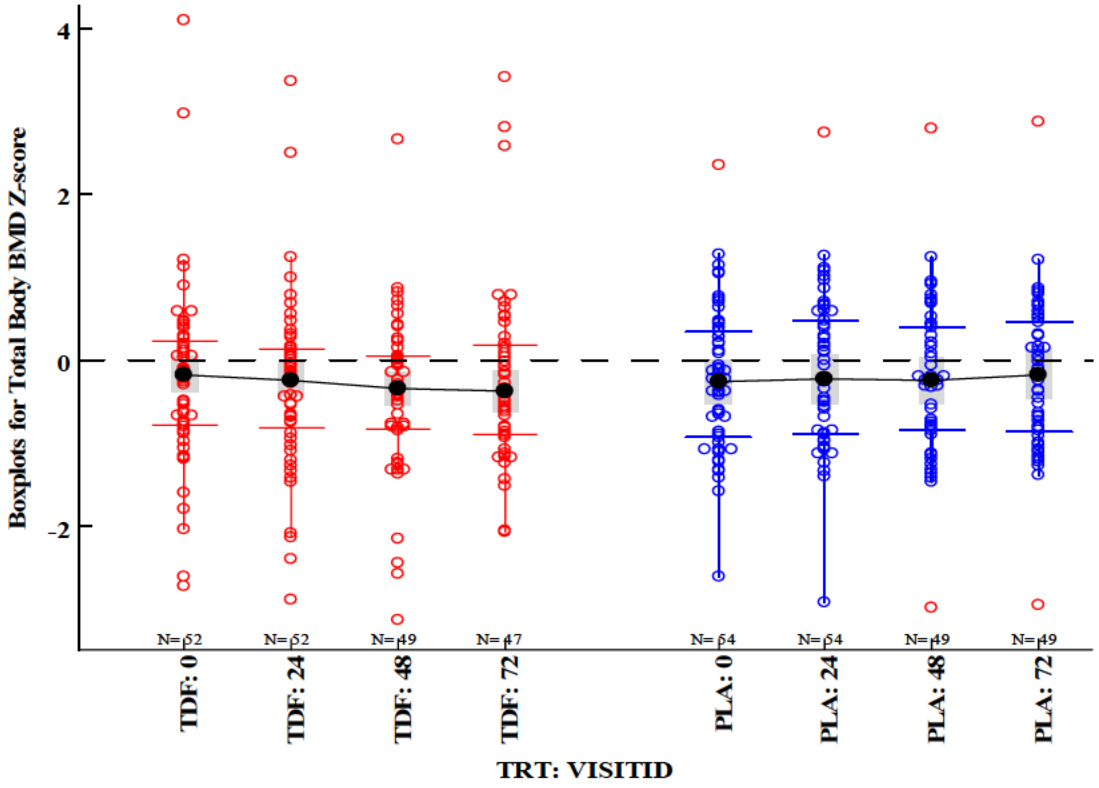
1-ANCOVA model for change from baseline with baseline z-score as the covariate. All results were computed by this reviewer.

At baseline, the average z-score for this population of HBV adolescent patients was less than zero indicating that BMD values were on average lower than the reference population; less than 25% of patients in each group had z-scores of -1 or less at baseline.

For both spine and whole body, TDF patients showed a decrease in z-score compared to placebo patients with a baseline-adjusted mean decrease over placebo of -0.1 for spine and -0.19 for whole body at Week 72 last-observation-carried-forward (LOCF, the LOCF results did not differ from the observed data results). The treatment difference for the whole body was statistically significant (p=0.01, ANCOVA with baseline as a covariate) while the difference for the spine was not significantly different (p=0.16). No patients in either group had a decrease of 1SD or more for either spine or whole body. About 60% of TDF patients had a decrease in z-score at Week 72 compared to less than 50% in the placebo group for both spine and whole body; this difference is not statistically significant (p=0.2, CMH).

Figure 3.2.1 illustrates the distribution of the whole body z-score data with boxplots and the decline in medians for TDF overtime compared to essentially no change in medians in the placebo group.

Figure 3.2.1 Study GS-US-174-0115 Boxplots of whole body BMD z-scores by treatment group and week



All patients were required to take a daily multivitamin which was provided by the study and contained 100% of the recommended daily requirement of vitamin D and then vitamin D levels were measured. About 75% of patients reported taking multivitamins during the trial. Increases of about 5 to 6 ng/mL in vitamin D levels were seen in both groups (Table 3.2.2). Changes in vitamin D levels were correlated with baseline vitamin D levels.

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).

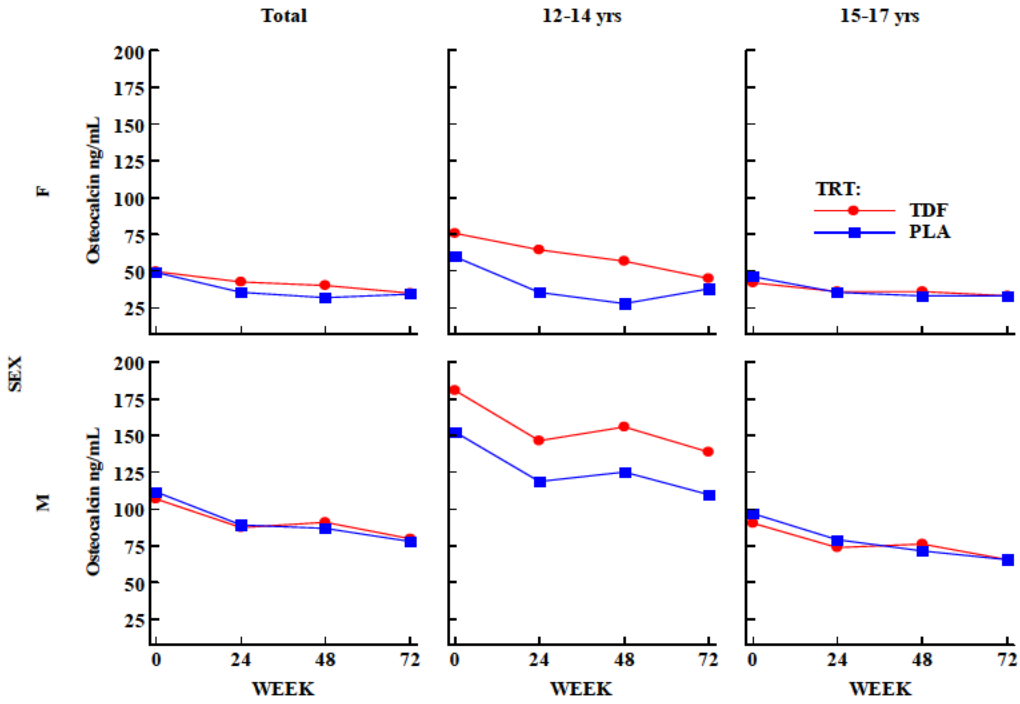
Table 3.2.6 Serum Osteocalcin (ng/mL) for HBV adolescent patients in Study GS-US-174-0115 and HIV adolescent patients in Study GS-US-104-0321

	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

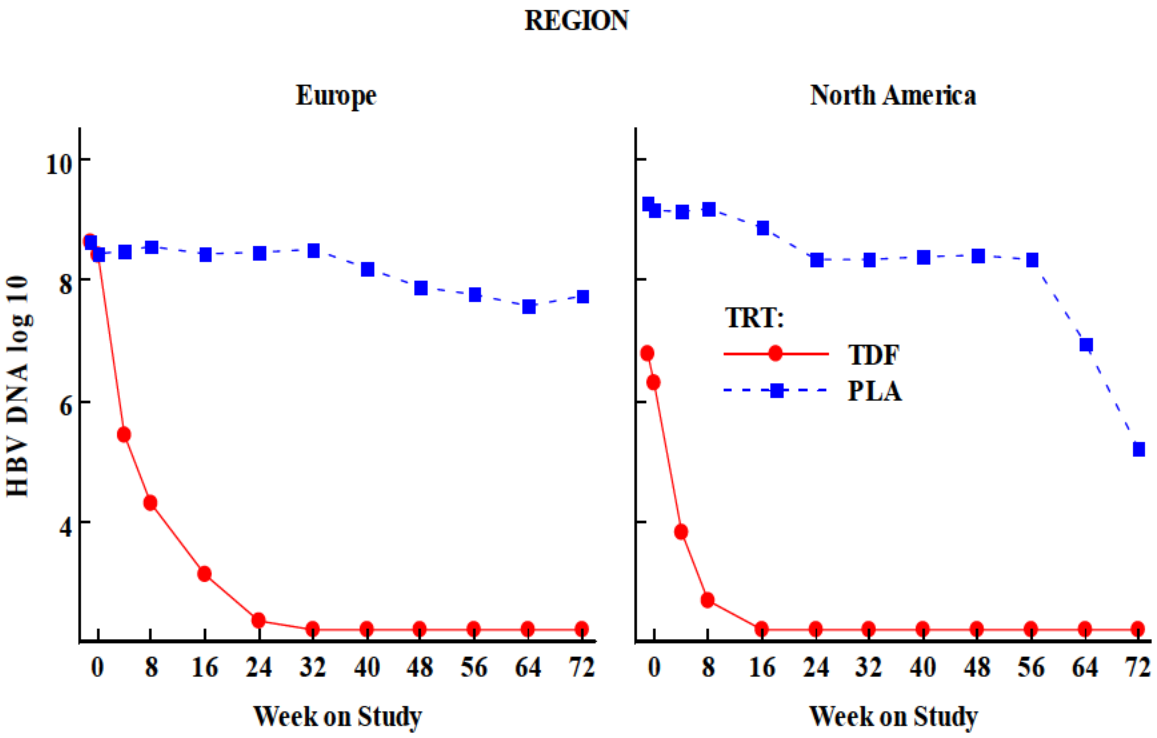
For the HIV population, the relationship between PTH changes and BMD changes was reported in the medical review as not correlated. For this HBV population, whole body BMD change from baseline at Week 72 is also not correlated with changes in PTH with an r^2 of about 0.2. So in both populations, there 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