CLINICAL REVIEW

Application Type	NDA
Application Number(s)	021356/S-042 and 022577/S-002
Priority or Standard	Priority
Submit Date(s)	February 17, 2012
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Division / Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Prabha Viswanathan, MD
Review Completion Date	July 24, 2012
Established Name	Tenofovir Disoproxil Fumarate
(Proposed) Trade Name	Viread®
Therapeutic Class	Nucleotide Analogue – inhibitor of Hepatitis B Virus Reverse Transcriptase
Applicant	Gilead Sciences, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	300 mg by mouth daily
Indication(s)	Treatment of chronic Hepatitis B Virus infection
Intended Population(s)	Adolescent patients ages 12 to <18 years of age, weighing 35 kg or more

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The safety and efficacy data submitted in this efficacy supplement support approval of tenofovir disoproxil fumarate (TDF, Viread®) for the treatment of Chronic Hepatitis B infection in adolescents aged 12 to < 18 years of age weighing ≥ 35 kilograms. From an efficacy standpoint, it was clear that subjects randomized to receive TDF were able to achieve viral suppression. The majority of the TDF subjects also normalized their ALT. Subjects randomized to receive placebo were unable to achieve spontaneous viral suppression and had a greater number of hepatic flares throughout the study.

1.2 Risk Benefit Assessment

As stated in the previous section, the efficacy results suggest clear benefit of TDF over placebo. Consistent with prior TDF trials, the results of DEXA scanning and biochemical assessments of bone turnover suggest negative effects on bone mineral density. However, the clinical significance of the TDF effect on bone metabolism is unclear, and longitudinal data will be needed to assess long-term effects on growth and fracture risk. Renal toxicity, which is well-described among HIV-1 infected patients, was not observed in this CHB study. No patients demonstrated significant decline in glomerular function or renal tubule injury. Review of the remainder of the safety data did not reveal any new or unexpected toxicities.

In conclusion, the benefit of tenofovir for the treatment of Chronic Hepatitis B infection outweighs the risks demonstrated in this study.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Although universal hepatitis B virus (HBV) vaccination is recommended in the United States and other parts of the world, chronic HBV (CHB) infection remains a significant global health problem resulting in chronic liver disease, cirrhosis, hepatocellular carcinoma and death. The majority of pediatric HBV infections in the US are the result

of vertical transmission, and up to 95% of patients with perinatal HBV infection are expected to develop chronic HBV infection. Among US pediatric patients with CHB, an estimated 5-10% spontaneously clear hepatitis B early antigen (HBeAg) each year. Upon HBeAg clearance, the infection usually becomes inactive, although a few will later reactivate.

Because the spontaneous clearance rate is significant but somewhat variable, there is no consensus regarding optimal timing of treatment in pediatric patients. To date, the only approved oral products for the treatment of CHB in pediatric patients include lamivudine (approved for patients ≥ 2 years of age), adefovir (approved for use in patients ≥ 12 years of age) and interferon alfa-2b (approved for patients ≥ 1 year of age). Each of these treatments has significant limitations including rapid development of resistance (lamivudine), renal toxicity that limits dosing (adefovir), and poor tolerability and safety profile (interferon alfa-2b). Therefore, better treatment options are needed for this population.

2.1 Product Information

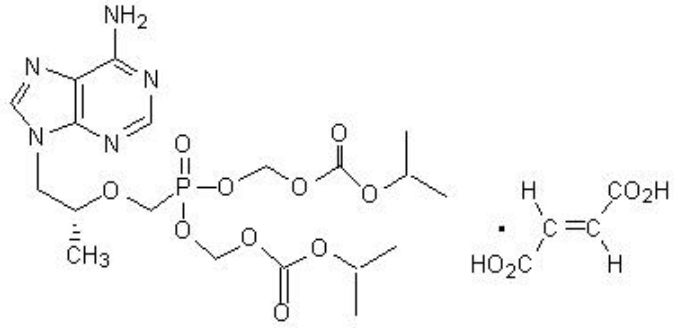
VIREAD® is the brand name for tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

Chemical name: 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy] propyl] adenine fumarate (1:1).

Molecular formula: $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$

Molecular weight: 635.52

Structural formula:



VIREAD® is available as tablets or as an oral powder.
VIREAD® tablets are for oral administration in strengths of 150, 200, 250, and 300 mg of TDF, which are equivalent to 123, 163, 204 and 245 mg of tenofovir disoproxil, respectively. Each tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The 300 mg tablets are coated with Opadry II Y–30–10671–A, which contains FD&C blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 150, 200, and 250 mg tablets are coated with Opadry II 32K-18425, which contains hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

VIREAD® oral powder is available for oral administration as white, taste-masked, coated granules containing 40 mg of TDF per gram of oral powder, which is equivalent to 33 mg of tenofovir disoproxil. The oral powder contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, ethylcellulose, and silicon dioxide [1].

2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved drugs for treatment of CHB are summarized in Table 1.

Table 1: Drugs Approved for Chronic Hepatitis B

Generic Name	Trade Name	Dose	Approved Ages
Interferon-alfa-2b	Intron A®	3 million IU/m^2 three times a week, followed by 6 million IU/m^2 three times a week. Max dose 10 million IU three times a week	≥ 1 year of age
Lamivudine	Epivir®	3 mg/kg once daily, maximum dose 100mg daily	≥2 years of age
Adefovir	Hepsera®	10 mg once daily	≥ 12 years of age
Entecavir	Baraclude®	0.5 mg once daily	≥ 16 years of age
Telbivudine	Tyzeka®	600 mg once daily	≥ 16 years of age

2.3 Availability of Proposed Active Ingredient in the United States

TDF is approved for the treatment of HIV-1 infection in adults and children ≥ 2 years of age, and for chronic HBV in adults. As such, it is widely available in the United States in tablet and powder formulations.

2.4 Important Safety Issues With Consideration to Related Drugs

TDF is a nucleotide reverse transcriptase inhibitor (NtRTI) and belongs to the class of nucleoside reverse transcriptase inhibitors (NRTI). Currently approved NRTIs for CHB, including telbivudine, entecavir, lamivudine, and adefovir, have a boxed warning cautioning about the risk of lactic acidosis, severe hepatomegaly with steatosis and severe acute exacerbations of Hepatitis B.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On October 11, 2007, Gilead Sciences submitted sNDA application 21-356/025 for the use of TDF to treat Chronic Hepatitis B infection in adults. The application was approved on August 11, 2008, resulting in required pediatric assessments mandated by the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

The pediatric population was divided into three age cohorts for the purpose of further studies: 12-18 years, 2 to < 12 years, and birth to < 2 years. The pediatric studies were deferred for the two older cohorts because the product was ready for approval for use in adults and the pediatric studies had not been completed. Studies in the youngest cohort were deferred because of concerns for bone toxicity in rapidly growing infants and young children. As such, the Agency determined that it would be prudent to review the studies in pediatric patients 2 to < 18 years age before determining whether it is appropriate to study TDF for HBV in the birth to <2 years age group. If the risk/benefit assessment from those studies is found to be unfavorable, then a waiver will be considered for the birth to < 2 years age group. In addition, since treatment for CHB is rarely initiated in the first two years of life, the Agency felt that this group may be waived in the future if this continues to be standard of care.

On December 21, 2011, the Agency granted Gilead Sciences a Written Request to investigate the potential use of TDF in the treatment of pediatric subjects 2 to < 18 years of age with chronic hepatitis B virus infection. The current submission is intended to fulfill a portion of that Written Request and PREA Post-Marketing Requirement (PMR) 283-1 (referenced above): Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 12 to < 18 years of age.

2.6 Other Relevant Background Information

Tenofovir was originally developed as a nucleotide reverse transcriptase inhibitor for treatment of HIV-1 infection. On October 26, 2001, tenofovir was approved for treatment of HIV-1 infection in adults in combination with other antiretroviral drugs (ARVs). A Written Request (PWR) was issued on December 21, 2001, which requested pharmacokinetic (PK), safety and efficacy studies in both ARV therapy-experienced and naïve pediatric patients. Findings from study GS-US-104-0321 led to approval for treatment of HIV-1 infection in patients >12 years of age in combination with other ARVs

on March 24, 2010 (sNDA 21356/S-033). Review of study GS-US-104-0352 subsequently extended the pediatric indication to children 2 years and greater on January 18, 2012 (sNDA 021356/S-038, NDA 022577/S-001).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was well organized and reasonable to navigate. Some clinical pharmacology datasets were not included with the original submission, but were provided in timely fashion upon request.

A consult request was made to the Office of Scientific Investigations (OSI) for inspection of 2 Polish sites. These sites were selected because they recruited a large proportion of the study population. Dr. Mizerski's site was audited between May 14 and May 18, 2012. Twenty-five patients were screened at this site, and 23 were randomized. The site was classified as Voluntary Action Indicated (VAI). The following comments are taken from the OSI memo:

> *A three items Form FDA 483 was issued, and discussed with the clinical investigator, who adequately responded to the inspectional findings in a letter dated June 4, 2012, in which he promised to implement corrective action plan. OSI finds his response acceptable.*

Dr. Szenborn's site, which screened 22 patients and randomized 16, was inspected on June 11 and 12, 2012. (b) (4)

3.2 Compliance with Good Clinical Practices

Study GS-US-174-0115 was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, protocol amendments, consent forms, and study subject information sheets were reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before study initiation. Investigators obtained written informed consent and patient assent from each participant.

3.3 Financial Disclosures

Gilead Sciences has submitted Form FDA 3454, which certifies that the Sponsor did not enter into any financial relationships with principle or sub-investigators. The form included an attachment containing the names of principal investigators and sub-investigators for study GS-US-174-0115 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no CMC related issues in this submission. The 300mg tablets studied in this trial are approved for use in adults with CHB and HIV-1 and are commercially available.

4.2 Clinical Microbiology

There was no evidence that tenofovir resistance had emerged during the study period. Please refer to Dr. Sung Rhee's Clinical Virology Review for full details.

4.3 Preclinical Pharmacology/Toxicology

TDF is an FDA-approved drug. No additional nonclinical data were submitted.

4.4 Clinical Pharmacology

A very brief discussion will be included here. Please refer to Dr. Dionna Green's review for full details.

4.4.1 Mechanism of Action

TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form the active drug, tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

4.4.2 Pharmacodynamics

Pharmacodynamic studies were not performed.

4.4.3 Pharmacokinetics

All subjects in the TDF group received TDF as a 300 mg tablet, administered once daily without regard to food. Tenofovir pharmacokinetics were assessed in all TDF-treated subjects in order to confirm the appropriateness of the 300-mg dose. Data were available from all 52 TDF subjects, and confirmed that the exposures resulting from this dose are comparable to those seen in HBV infected adults, and HIV-infected children and adults.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Pediatric Clinical Trials of TDF Analyzed or Referenced in Support of this Submission

Study Identifier and Location	Type of Study	Objectives	Study Design	Study and Control Drug Regimen	Number of Subjects	Population Studied
Hepatitis B						
GS-US-174-0115 21 sites: Poland 8 Romania 3 US 3 Bulgaria 2 France 2 Spain 2 Turkey 1	Safety and Efficacy	Evaluate safety and efficacy of TDF vs. placebo in adolescents (aged 12–17 years) with CHB	Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial	Group 1: TDF 300 mg po daily Group 2: placebo po daily	106 (ITT)	TDF-naïve adolescents aged 12–17 years with compensated CHB
HIV						
GS-US-104-0321 18 sites: Brazil 17, Panama 1	Safety and Efficacy	Assess safety and efficacy of TDF plus optimized background regimen (OBR) vs. placebo plus OBR in HIV-1	Randomized double-blind, placebo-controlled, multicenter, phase 3 trial	Group1: TDF 300mg po daily + OBR Group 2: Placebo po daily+ OBR	87 randomized and treated; 85 analyzed for efficacy	Treatment experienced adolescents aged 12 - 17 years on a failing ARV regimen, with plasma HIV-1 RNA viral load >1000 cps/mL

		infected, treatment experienced adolescents on a failing ARV regimen				
GS-US-104-0352 9 sites: US 6, Panama 1, UK 1	Safety and Efficacy	Evaluate safety, tolerability, PK, and efficacy of TDF for virologically suppressed HIV-1 infected children	Randomized, open-label, multicenter pediatric trial	Group 1: TDF tablets (weight band) or powder (8mg/kg) po daily + HAART Group 2: d4T or ZDV + HAART	97 enrolled; 92 (ITT)	Pediatric subjects aged 2 to < 12 with documented HIV-1 infection who were virologically suppressed (plasma HIV-1 RNA < 400 copies/mL) at baseline on their d4T- or ZDV-containing highly active antiretroviral therapy (HAART) regimen

5.2 Review Strategy

Prior to analyzing the data in this submission, the current literature regarding treatment of Hepatitis B in pediatric patients was reviewed. Then, in order to gain a better understanding of tenofovir, prior pediatric TDF submissions for the HIV indication were reviewed.

The data in this submission come from a single study. The safety review was conducted first, with an emphasis on bone and renal toxicity, followed by the efficacy review. Statistical analyses were performed using JMP, and the results were compared to those provided by the Sponsor. Any discrepancies were discussed with the primary statistical reviewer, Joy Mele.

5.3 Discussion of Individual Studies/Clinical Trials

Study GS-US-174-0115 was a Phase 3, multi-center, randomized, double-blind study of the antiviral efficacy, safety, and tolerability of Tenofovir Disoproxil Fumarate (TDF) versus placebo in adolescents 12 to <18 years of age with chronic Hepatitis B (CHB) infection. CHB is defined as the presence of HBsAg for > 6 months. In addition to this basic criteria, subjects also had to demonstrate HBV deoxyribonucleic acid (DNA) ≥ 10^5 copies/mL AND either alanine aminotransferase (ALT) ≥ 2 × the upper limit of normal (ULN) at screening OR any history of ALT ≥ 2 × ULN over the past ≤ 24 months.

The primary objective of this study was to compare the antiviral efficacy, safety and tolerability of TDF 300 mg once daily versus placebo once daily in adolescents aged 12 to < 18 years with chronic hepatitis B infection. The secondary objectives of this study

were: to evaluate the biochemical and serological responses to TDF versus placebo in adolescents with chronic hepatitis B infection; and to evaluate the incidence of drug resistance mutations.

Subjects who met the eligibility criteria were randomized 1:1 to receive TDF 300mg po daily or placebo (PLB). Randomization was stratified by age (12 to 14 years and 15 to 17 years) and geographical location of study site (North America, Europe). Subjects must have been naïve to TDF, but could have received interferon or oral anti-HBV nucleoside/nucleotide therapy. Subjects were eligible regardless of their Hepatitis B early Antigen (HBeAg) status.

Inclusion Criteria
Subjects who met ALL of the following criteria were eligible for participation.

- Male or female
- 12 through 17 years of age, inclusive (consent of parent/legal guardian required)
- HBeAg-positive or HBeAg-negative (a maximum of 50% of subjects may have been HBeAg-negative)
- Weight ≥ 35 kg
- Able to swallow oral tablets
- HBV DNA ≥ 10^5 copies/mL (PCR method)
- ALT ≥ 2 × ULN at screening, OR any history of ALT ≥ 2 × ULN over the past ≤ 24 months
- Willing and able to provide written informed consent/assent (child and parent/legal guardian)
- Negative serum β-human chorionic gonadotropin (HCG) pregnancy test (for postmenarchal females only)
- Estimated glomerular filtration rate (creatinine clearance) ≥ 80 mL/min/1.73m^2
  Estimated creatinine clearance using Schwartz Formula
  (mL/min/1.73m^2) = k × L/Scr
  k is a proportionality constant: for adolescent females ≥ 12 years old, k = 0.55, and for adolescent males ≥ 12 years, k = 0.70; L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)
- Adequate hematologic function (absolute neutrophil count ≥ 1,500/mm^3; hemoglobin ≥ 10.0 g/dL)
- No prior TDF therapy (subjects may have received prior interferon or oral anti-HBV nucleoside/nucleotide therapy; subjects must have discontinued interferon therapy ≥ 6 months prior to screening; subjects experienced on anti-HBV nucleoside/nucleotide therapy must have discontinued therapy ≥ 16 weeks prior to screening to avoid flare if randomized to the placebo group)

Exclusion Criteria
Subjects who met ANY of the following criteria were ineligible for participation.

- Pregnant women, women who were breast feeding or wished to become pregnant during the course of the study
- Sexually-active males and females of reproductive potential who were not willing to use an effective method of contraception during the study. For males, condoms should have been used and for females, a barrier contraception method should have been used in combination with one other form of contraception
- Decompensated liver disease defined as direct (conjugated) bilirubin > 1.2 × ULN, prothrombin time (PT) > 1.2 × ULN, platelets < 150,000/mm^3, serum albumin < 3.5 g/dL, or prior history of clinical hepatic decompensation (eg, ascites, jaundice, encephalopathy, variceal hemorrhage)
- Receipt of interferon (pegylated or not) therapy within 6 months of the Screening Visit
- Receipt of anti-HBV nucleoside/nucleotide therapy within 16 weeks of the Screening Visit
- α-fetoprotein > 50 ng/mL
- Evidence of HCC
- Co-infection with HIV, HCV, or HDV
- History of significant renal disease (ex: nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis, acute tubular necrosis, other renal disease)
- History of significant bone disease (ex:, osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses, multiple bone fractures)
- Significant cardiovascular, pulmonary or neurological disease
- Evidence of a gastrointestinal malabsorption syndrome that may have interfered with absorption of orally administered medications
- Ongoing therapy with any of the following:
  - Nephrotoxic agents
  - Parenteral aminoglycoside antibiotics
  - Cidofovir
  - Cisplatin
  - Foscarnet
  - Intravenous (IV) amphotericin B
  - IV pentamidine
  - Oral or IV ganciclovir
  - Cyclosporine
  - Tacrolimus
  - IV vancomycin
  - Chronic daily non-steroidal anti-inflammatory drug therapy
  - Competitors of renal excretion (ex: probenecid)
  - Systemic chemotherapeutic agents
  - Systemic corticosteroids

- Interleukin-2 (IL-2) and other immunomodulating agents
- Investigational agents (except with the expressed approval of the Sponsor)

Administration of any of the above medications must have been discontinued at least 30 days prior to the Baseline Visit and for the duration of the study period.

- History of solid organ or bone marrow transplantation
- Known hypersensitivity to the study drugs, the metabolites or formulation excipients
- Any other condition (including alcohol or substance abuse) or prior therapy that, in the opinion of the Investigator, would have made the subject unsuitable for the study or unable to comply with dosing requirements

Study Design

Subjects who met the eligibility criteria were randomized in a 1:1 ratio to treatment group A or B:
Treatment A: blinded TDF 300 mg orally (PO) once daily
Treatment B: blinded matching placebo PO once daily

In addition, all subjects were required to take a daily multivitamin containing 100% of the recommended daily allowance of vitamin D. A minimum calcium requirement was not specified.

The double-blind, randomized phase of the study was 72 weeks, followed by an open-label follow-on phase for an additional 120 weeks (2.5 years). The duration of the study overall will be at least 4 years, with each patient receiving a total of 192 weeks of therapy.

The Screening Visit was the first study visit, and included obtaining informed consent, medical history and comprehensive physical exam, laboratory work, and AE review. The Screening Visit was followed by a Baseline Visit, which included a comprehensive physical exam, laboratory work, Dual energy x-ray absorptiometry (DEXA) scanning, AE and adherence review, and dispensation of study drug. This was followed by 2 visits at 4 week intervals, and then 8 visits at 8 week intervals. These visits included abbreviated physical examinations, laboratory work, AE and adherence review, and dispensation of study drug. Assessments of bone health (DEXA scanning and biochemical markers of bone turnover) were conducted at baseline and Weeks 24, 48, and 72. Table 3 provides full details of each study visit.

Table 3: Schedule of Assessments

Study Procedures	Screening[a]	Baseline	Study Week 4	8	16	24	32	40	48	56	64	72	Early DC	24-Wk FU
Written Informed Consent, Subject Assent	X													
Medical History	X	X												
Complete Physical Examination	X	X				X			X			X	X	
Symptom-Directed Physical Examination			X	X	X		X	X		X	X			X
Vitals Signs, Height, Weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1, HCV, HDV, α-fetoprotein	X													
HBV DNA Levels (PCR-Based Assay)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV Serology[f]	X	X			X		X		X		X	X	X	X
HBV Genotyping, Resistance Surveillance[h]		X							X			X	X	
Hematology Profile	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry and Liver Tests[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prothrombin Time/INR[j]	X	X												X[j]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma for TDF Concentration		X	X	X	X	X	X	X	X	X	X	X	X	
Serum and Plasma for Storage[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DEXA Scan – Spine and Whole-Body[m]		X				X			X			X	X[n]	
Serum Bone Biochemical Markers[o]	X	X				X			X			X	X[n]	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing/Return[p]		X	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability/Adherence Assessment			X	X	X	X	X	X	X	X	X	X	X	

Source: Sponsor CSR Section 7.5.1, Table 7-2

Laboratory Studies:
Subjects underwent laboratory evaluation at regular intervals to measure disease activity and to screen for toxicity. Disease-specific assessments included HBV DNA PCR, HBV serology, HBV genotyping, hepatic function tests, and coagulation studies. Renal toxicity surveillance included urinalysis and metabolic panel. Bone toxicity surveillance included DEXA scanning and bone biochemical markers, including N-telopeptide, C-telopeptide, osteocalcin, bone specific alkaline phosphatase, vitamin D (25-hydroxy), and parathyroid hormone. Treatment adherence was assessed via plasma TDF concentration and compared with the adherence assessment. Pregnancy tests were performed in females. CBC was also routinely monitored.

Early Discontinuation

Subjects who experienced Grade 4 ALT while on blinded study medication were evaluated weekly with serum chemistry and liver function test monitoring. In the event that any subject had sustained Grade 4 ALT for ≥ 16 weeks (ie, failure to resolve ALT to Grade ≤ 3 or baseline), the serial HBV DNA values were provided to the investigator and the subject could be offered open-label TDF, after discussion with the Sponsor's medical monitor.

Subjects who permanently discontinued study drug were asked to return for an end-of-treatment visit within 72 hours of the last dose of study drug. Subjects who permanently discontinued study drug were followed for 24 weeks off treatment or up to initiation of active treatment, whichever occurred first. For subjects off treatment, post-treatment follow-up evaluations, ie, serum chemistry, liver function tests, and plasma HBV DNA, were performed every 4 weeks.

Safety Monitoring

Adverse Events (AEs):

All AEs were assessed by the investigator and recorded on the AE Case Report Form (CRF) page. The AE entry should have indicated whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or to a study procedure, the action taken with study drug due to the AE, and the severity of the AE. The relationship to study drug therapy should have been assessed using clinical judgment and standard definitions.

Serious Adverse Events (SAEs)

SAEs were defined using standard criteria: death, life-threatening situations, hospitalization, persistent/significant disability, congenital anomalies in the offspring of a study subject, and other medically significant events that may have jeopardized the subject. In addition, the following study-specific situations were defined as SAEs:

- Serum ALT > 2 × baseline and > 10 × ULN, with or without associated symptoms.
- Confirmed ALT elevation (defined as 1-grade shift or 2 × previous value) associated with confirmed changes outside of the normal range in other laboratory parameters suggestive of worsening hepatic function: total bilirubin ≥ 2 mg/dL above baseline, abnormal PT ≥ 2 seconds or INR ≥ 0.5 over baseline, abnormal serum albumin ≥ 1 g/dL below baseline or elevated serum lactate levels (if available), defined as 2 × ULN per the Adult AIDS Clinical Trials Group (AACTG) guidelines.
- Any clinical manifestations of hepatic decompensation (variceal bleeding, hepatic encephalopathy, or worsening of ascites requiring diuretics or paracentesis).

Study Investigators were provided specific guidelines for toxicity management, based on the grade of the AE/SAE. In addition, protocols were established for managing renal insufficiency, hepatic flares, and changes in bone mineral density.

Data Monitoring Committee (DMC)
An external independent multidisciplinary DMC reviewed the progress and safety of this study every 24 weeks after the first subject was randomized. At each meeting, the DMC reviewed routine safety and DEXA data and made recommendations regarding modification of study treatment.

Analysis Sets
The Full Analysis Set (FAS) included all subjects who were randomized into the study and received at least 1 dose of study drug (TDF or PLB). The FAS was the primary analysis set for all efficacy analyses. Subjects discontinuing randomized therapy prior to Week 72 were handled using a double-blind efficacy evaluation (DBEE) algorithm for the purpose of the primary efficacy analysis and all analyses of categorical secondary efficacy endpoints.

The Safety Analysis Set (SAS) included all subjects who received at least 1 dose of study medication and was the primary analysis set for all safety analyses in the Week 72 end of double-blinded treatment analysis.
The pharmacokinetic (PK) analysis set included all subjects who were treated with TDF (during the double-blinded or open-label period) and had evaluable concentrations at the time points of interest.

6 Review of Efficacy

Efficacy Summary

Study GS-US-174-0115 is a Phase 3, multi-center, randomized, double-blind study of the antiviral efficacy, safety, and tolerability of TDF versus placebo in adolescents 12 to <18 years of age with CHB. The primary efficacy endpoint, HBV DNA < 400 copies/ml at Week 72, is a surrogate marker that is often used in pediatric CHB trials. The study was designed such that a sample size of 100 patients (50 in each group) would provide at least 80% power to detect a difference of 30% between treatment groups.

The treatment groups were well-matched with respect to baseline demographic and disease characteristics. Fifty-two patients were randomized to TDF and 54 to PLB. There was a high rate of study retention, with 51 TDF patients and 50 PLB patients completing the Week 72 assessment.

The study met its primary endpoint. At Week 72, 88.5% of patients randomized to TDF had an HBV viral load < 400 copies/ml, whereas none of the placebo patients were able to achieve this endpoint. Mean viral load at Week 72 was 2.6 $\log_{10}$ copies/ml for the

TDF group and 7.2 $\log_{10}$ copies/ml for the PLB group. Patient non-adherence (suggested by low plasma TDF concentrations) was largely responsible for lack of viral suppression in the TDF patients who did not achieve the primary endpoint. Viral resistance surveillance did not detect any tenofovir resistance mutations.

Several secondary endpoints were also assessed at Week 72. TDF demonstrated superiority to PLB in the proportion of patients with HBV DNA < 169 copies/ ml (TDF 84.6%, PLB 0%, p-value <0.001) and normal ALT (TDF 76.9%, PLB 38.9%, p-value <0.001). The two treatment groups had a similar rate of HBeAg loss (TDF 20.8, PLB 14.6, p-value 0.41). One TDF patient had sustained loss of HBsAg and demonstrated seroconversion.

6.1 Indication

Viread® is currently approved for the treatment of chronic Hepatitis B infection in adults. With this submission, the applicant seeks to extend this indication to adolescents ages 12 to <18 years of age who weigh 35 kg or more.

6.1.1 Methods

Please refer to section 5.3 for details regarding the study design.

Primary and secondary efficacy endpoints were identified prior to study commencement, as follow:

The primary efficacy endpoint was HBV DNA < 400 copies/mL at Week 72.

For Weeks 48 and 72, the following secondary endpoints were evaluated. However, Week 48 endpoints were not analyzed prior to the primary efficacy analysis.

- For all subjects, secondary endpoints included ALT normal; 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 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.

For the primary endpoint and categorical secondary efficacy endpoints, missing data was handled using a long-term evaluation of efficacy intention-to-treat algorithm.

Genotypic changes from baseline within the HBV polymerase were analyzed for subjects with HBV DNA ≥ 400 copies/mL at Weeks 48 and/or 72, subjects who experienced virologic breakthrough, or subjects who discontinued early (after Week 24 with HBV DNA ≥ 400 copies/mL).

Medical Officer Comment: The study was well-designed to meet its objectives and measure the pre-determined endpoints. Primary analyses of safety and efficacy data were performed using JMP, and the results were compared to the analyses provided by the Sponsor. No major discrepancies were found.

6.1.2 Demographics

The study period began on December 3, 2008 (first subject screened) and ended on March 1, 2011 (last subject observation recorded). There were 21 enrolling centers, the majority of which were in Europe: Poland (8), Romania (3), the United States (3), Bulgaria (2), France (2), Spain (2), and Turkey (1).

One hundred-six TDF-naive adolescents aged 12 to 17 years with chronic HBV infection were randomized in a 1:1 ratio to treatment group A or B:

Treatment A: blinded TDF 300 mg PO once daily – 52 subjects
Treatment B: blinded matching placebo PO once daily – 54 subjects

Baseline demographic characteristics are summarized in Table 4.

Table 4: Baseline Demographic Characteristics

	TDF		Placebo		Total		
	12-14 yrs	**15-17 yrs**	**12-14 yrs**	**15-17 yrs**	**TDF**	**Placebo**	**Overall**
Age (years)							
n	10	42	13	41	52	54	106
Mean (SD)	13.3 (0.8)	16.1 (0.8) 15,	13.2 (0.7)	15.9 (0.8)	15.5 (1.3)	15.3 (1.4)	15.4 (1.4)
Min, Max	12, 14	17	12, 14	15, 17	12, 17	12, 17	12, 17
Sex n (%)							
Male	7 (70)	31 (73.8)	9 (69.2)	26 (63.4)	38 (73.1)	35 (64.8)	73 (68.9)
Female	3 (30)	11 (26.2)	4 (30)	15 (36.6)	14 (26.9)	19 (35.2)	33 (31.1)

Race n (%)							
White	10 (100)	39 (92.9)	12 (92.3)	37 (90.2)	49 (94.2)	49 (90.7)	98 (92.5)
Other	0	1 (2.4)	0	4 (9.8)	1 (1.9)	4 (7.4)	5 (4.7)
Asian	0	1 (2.4)	1 (7.7)	0	1 (1.9)	1 (1.9)	2 (1.9)
Black	0	1 (2.4)	0	0	1 (1.9)	0	1 (0.9)
Region n (%)							
Europe	10 (100)	40 (95.2)	12 (92.3)	39 (95.1)	50 (96.2)	51 (94.4)	101 (95.3)
Poland	6 (60)	31 (73.4)	6 (46.2)	31 (75.6)	37 (71.1)	37 (68.5)	74 (69.8)
Romania	4 (40)	4 (9.5)	2 (15.4)	4 (9.8)	8 (15.4)	6 (11.1)	14 (13.2)
Bulgaria	0	3 (7.1)	3 (23.1)	1 (2.4)	3 (5.8)	4 (7.4)	7 (6.7)
France	0	1 (2.4)	0	1 (2.4)	1 (1.9)	1 (1.9)	2 (1.9)
Turkey	0	1 (2.4)	1 (7.7)	0	1 (1.9)	1 (1.9)	2 (1.9)
Spain	0	0	0	2 (4.9)	0	2 (3.7)	2 (1.9)
USA	0	2 (4.9)	1 (7.7)	2 (4.9)	2 (3.8)	3 (5.6)	5 (4.7)
Weight (kg)							
n	10	42	13	41	52	54	106
Mean	50	63.9	52	59.8	61.2	57.9	59.5
(SD)	(9.3)	(11.3)	(10.5)	(11.1)	(12.2)	(11.3)	(11.8)
Min, Max	35.6, 71	46.5, 93	38, 73	39.6, 91	35.6, 93	38, 91	26.5, 93
Height (cm)							
n	10	42	13	41	52	54	106
Mean	162.9	172	163	170.2	170.3	168.5	169.4
(SD)	(8.4)	(8.1)	(10.9)	(8.2)	(8.9)	(9.4)	(9.1)
Min, Max	148, 178	156, 187	149, 179	154, 188	148, 187	149, 188	148, 188
BMI (kg/m^2)							
n	10	42	13	41	52	54	106
Mean	18.8	21.6	19.5	20.6	21.1	20.3	20.7
(SD)	(2.9)	(3.8)	(2.7)	(3.1)	(3.8)	(3)	(3.4)
Min, Max	16.3,25.2	15.9,34.2	15.6,24.7	16, 31.4	15.9,34.2	15.6,31.4	15.6,34.2

Medical Officer Comment: The two treatment groups are evenly matched. However, the study population overall is skewed in that white males comprise the majority in the older cohort. In addition, the bulk of the study population was recruited in Eastern Europe, and included only 5 North American subjects. Since data from previous TDF trials in HIV infected individuals have not revealed major differences in the metabolism or activity of TDF, the results of this data should be fully generalizable to the US population, but the demographic imbalances should be noted.

The study population's baseline disease characteristics are summarized in Table 5.

Table 5: Baseline Disease Characteristics

	TDF		Placebo		Total		
	12-14 yrs	**15-17 yrs**	**12-14 yrs**	**15-17 yrs**	**TDF**	**Placebo**	**Overall**
HBV DNA (log_{10}cp/ml)							
N	10	42	13	41	52	54	106
Mean	8.26	7.95	8.61	8.12	8.01	8.24	8.13
(SD)	(1.5)	(1.4)	(1.17)	(1.5)	(1.4)	(1.4)	(1.4)
Min, Max	5.5, 10.1	4.9, 9.8	6.2, 10.1	4.8, 10	1.8, 10.1	4.8, 10.1	4.8, 10.1
ALT (U/L)							
N	10	42	13	41	52	54	106
Mean	77	106	101	101	101	101	101
(SD)	(54.8)	(116.4)	(95.4)	(89.5)	(107.5)	(90)	(98.5)
Min, Max	21, 207	19, 563	16, 359	20, 501	19, 563	16, 501	16, 563
N (%) Normal ALT	3 (30)	14 (33.3)	4 (30.8)	8 (19.5)	17 (32.7)	12 (22.2)	29 (27.4)
AST (U/L)							
N	10	42	13	41	52	54	106
Mean	53	66	82	62	64	67	66
(SD)	(33.1)	(73.6)	(108.6)	(46.6)	(67.7)	(66.2)	(66.7)
Min, Max	21, 134	18, 432	20, 432	18, 261	18, 432	18, 432	18, 432
HBeAg N (%)							
Positive	9 (90)	39 (92.9)	13 (100)	35 (85.4)	48 (92.3)	48 (88.9)	96 (90.6)
Anti HBe Ab N (%)							
Positive[1]	1 (10)	3 (7.1)	0	6 (14.6)	4 (7.7)	6 (11.1)	10 (9.4)
HBsAg[2] N (%)							
Positive	10 (100)	42 (100)	13 (100)	41 (100)	52 (100)	54 (100)	106(100)
HBV Genotype n (%)							
A	5 (50)	30 (71.4)	5 (38.5)	29 (70.7)	35 (67.3)	34 (63)	69 (65.1)
D	5 (50)	10 (23.8)	7 (53.8)	11 (26.8)	15 (28.8)	18 (33.3)	33 (31.1)
B	0	1 (2.4)	1 (737)	1 (2.4)	1 (1.9)	2 (3.7)	3 (2.8)
C	0	1 (2.4)	0	0	1 (1.9)	0	1 (0.9)

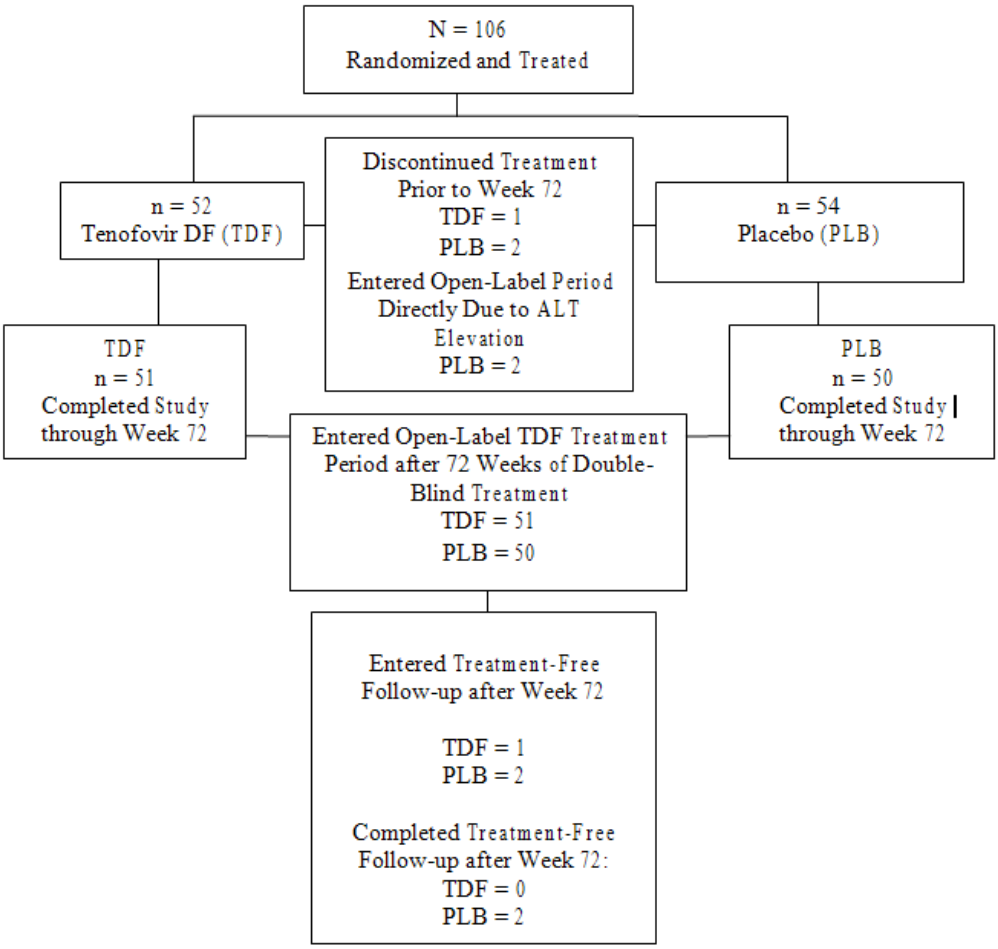
1 Remaining values are MISSING, not NEGATIVE
2 Anti HBs Ab was not assessed

Medical Officer Comment: The two treatment groups are evenly matched.

6.1.3 Subject Disposition

Figure 1 outlines the flow of subjects through the study.

Figure 1: Subject Disposition



Source: Sponsor CSR Section 8.1, Figure 8-1

Medical Officer Comment: The vast majority of randomized subjects completed the study. One TDF patient discontinued the study early due to syncopal events. This patient had a history of syncope predating the study. A total of 4 PLB subjects discontinued the randomized phase early, of which 2 subjects were transitioned to open-label TDF due to sustained ALT elevations. The loss of these subjects has minimal effect on the interpretability of the study results.

6.1.4 Analysis of Primary Endpoint(s)

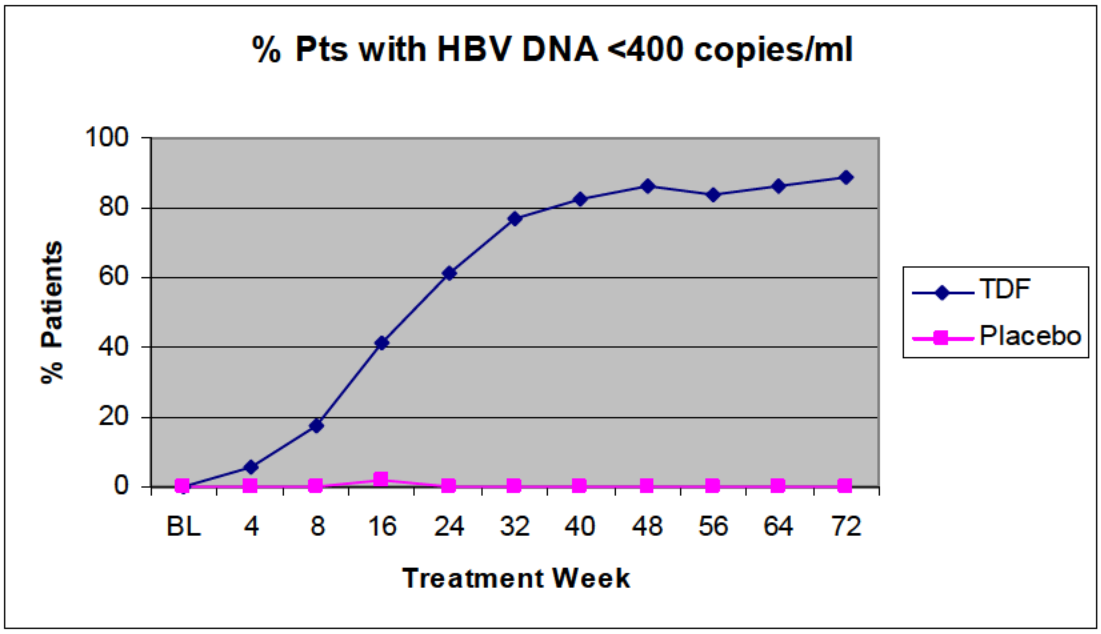
The primary endpoint was the proportion of subjects with HBV DNA <400 copies/ml at Week 72, which was the end of the randomized double-blind treatment. There was a marked difference between treatment groups: no placebo subjects and 88.5% of TDF subjects achieved the endpoint ($p < 0.001$).

Table 6 shows the percentage of subjects in each treatment arm that attained viral suppression over time. The same data are graphically represented in Figure 2.

Table 6: Percent of Pts with HBV DNA < 400 copies/ml, by Study Week

	Treatment Arm	
Study Week	**TDF N=52**	**Placebo N=54**
Baseline	0	0
4	5.8	0
8	17.3	0
16	41.2	2
24	61.5	0
32	76.9	0
40	82.7	0
48	86.5	0
56	84	0
64	86.5	0
72	88.5	0

Figure 2: Percent of Subjects over Time who Achieve the Primary Efficacy Endpoint of HBV DNA <400 copies/ml

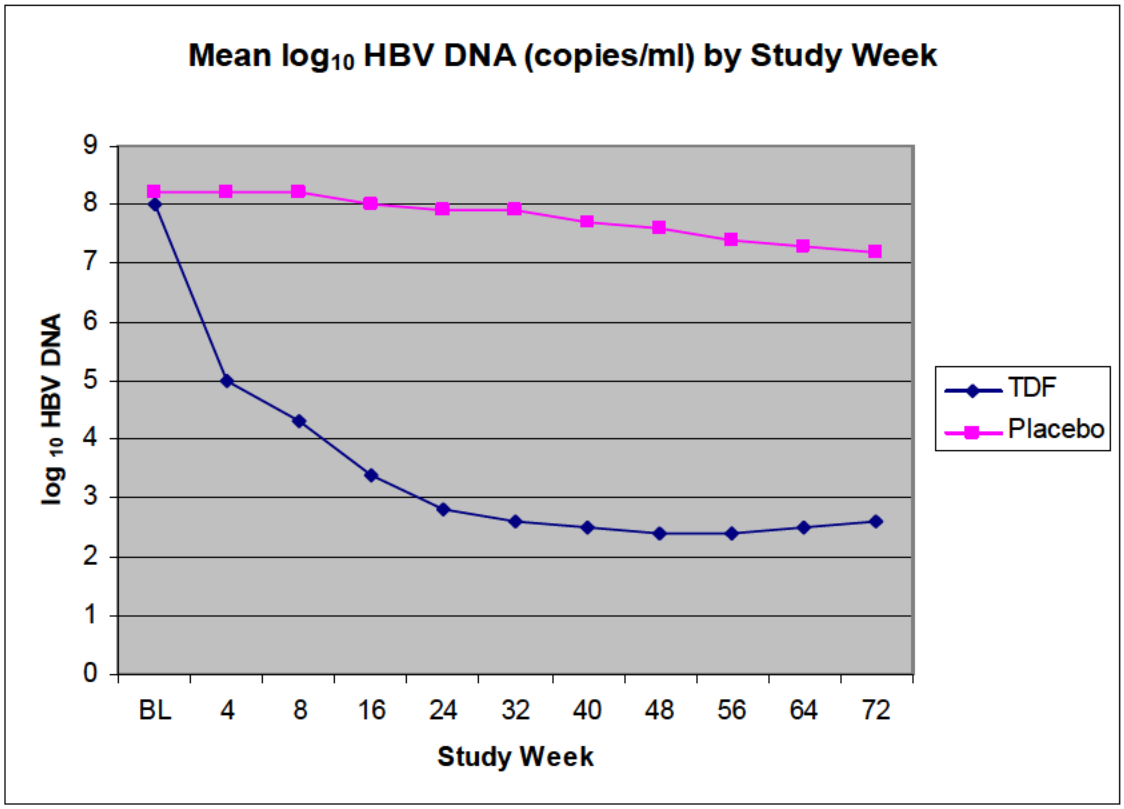


The majority of subjects who received TDF rapidly attained viral suppression, with the most precipitous decline in viral load occurring during the first 8 weeks of therapy. This was followed by a more gradual decline over the next 16 weeks. From Week 24 onwards, the treatment effect largely plateaued. Table 7 and Figure 3 describe the reduction in viral load over time.

Table 7: Mean $\log_{10}$ HBV DNA (copies/ml), by Study Week

	Treatment Arm	
Study Week	**TDF N=52**	**Placebo N=54**
Baseline	8	8.2
4	5	8.2
8	4.3	8.2
16	3.4	8
24	2.8	7.9
32	2.6	7.9
40	2.5	7.7
48	2.4	7.6
56	2.4	7.4
64	2.5	7.3
72	2.6	7.2

Figure 3: Virologic Response over Time



Resistance Analysis
The subjects who did not achieve the primary efficacy endpoint were further scrutinized to determine the etiology of their treatment failure. Genotypic and phenotypic analyses were performed to determine whether treatment-emergent resistance polymorphisms had developed. PK data were also analyzed to determine whether treatment failure was related to non-adherence with medication.

Five subjects in the tenofovir group had HBV DNA >400 copies/ml at Week 72. Subject 3990-7003 had never achieved a viral load < 400 copies/ml, but had a 6.86 $\log_{10}$ reduction from baseline. The remaining 4 subjects (1404-8029, 1404-8032, 1404-8070, and 1404-8077) had achieved viral loads <400 copies/ml and experienced virologic breakthrough. In each case, the breakthrough could be attributed to nonadherence, as indicated by low plasma tenofovir levels.

Genotypic analysis of the 5 subjects that qualified for testing demonstrated that 2 subjects had no change from baseline, 2 subjects had unique polymorphic site changes, and 1 subject had a reversion at a conserved site of a mixture back to wild-type. Their changes are summarized in Table 8.

Table 8: Genotypic Analysis

Subject ID	Baseline HBV DNA[a]	HBV DNA at Week 72[a]	Resistance Surveillance at Week 72[b]
Subject 3990-7003	10.11	3.25	No Change From Baseline
Subject 1404-8029	5.47	3.87	(b) (6)
Subject 1404-8032	9.30	8.96	(b) (6)
Subject 1404-8070	9.81	10.02	No Change From Baseline
Subject 1404-8077	5.55	5.72	(b) (6)

a HBV DNA is expressed as $\log_{10}$ copies/mL

b Conserved site changes are noted in **bold with brackets**

Source: Sponsor's CSR, Table 9-9

The HBV from subjects with confirmed virologic breakthrough or who developed conserved site changes in HBV pol/RT were analyzed phenotypically. All HBV isolates tested showed full susceptibility to tenofovir indicating that no tenofovir resistance had developed among these subjects.

Medical Officer Comments: These data clearly demonstrate that the study achieved its primary efficacy endpoint. There is a profound difference in treatment effect between the two groups. Subjects who received TDF experienced a rapid reduction in viral load and were able to sustain viral suppression over the entire study period. As expected, subjects who received placebo did not spontaneously clear the virus. One patient (2%) in the placebo arm had an HBV PCR <400 copies/ml at Week 16, but rebounded with a higher viral load for the remainder of the study. This could represent transient clearing of virus, or may have been a laboratory error. Details of the case are limited.

Inquiry into the 5 tenofovir subjects who did not achieve the primary endpoint reveals that tenofovir was, in fact, an effective treatment. Four of the five subjects had achieved viral suppression at some point during the study and experienced virologic breakthrough as a result of treatment-nonadherence. The fifth patient had experienced a substantial decrease in his viral load, but was unable to achieve the threshold of < 400 copies/ml.

6.1.5 Analysis of Secondary Endpoints(s)

Several secondary efficacy endpoints were evaluated in this study, at both Week 48 and Week 72:

- For all subjects, secondary endpoints included ALT normal; 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 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.

For the purpose of this review, not all secondary endpoints will be analyzed. All of the composite endpoints included the primary endpoint of HBV DNA < 400 copies/ml, and since the placebo group failed this endpoint, the group subsequently failed all composite secondary endpoints (briefly discussed in Section 6.1.6). In this section, attention will be focused on the individual, non-composite endpoints:

- Percent of subjects with HBV DNA < 169 copies/ml
- Percent of subjects with normal ALT
- Percent of subjects with abnormal ALT at baseline who attained a normal ALT
- Percent of subjects with HBeAg loss and seroconversion (pertains only to those subjects who were HBeAg positive at study baseline).

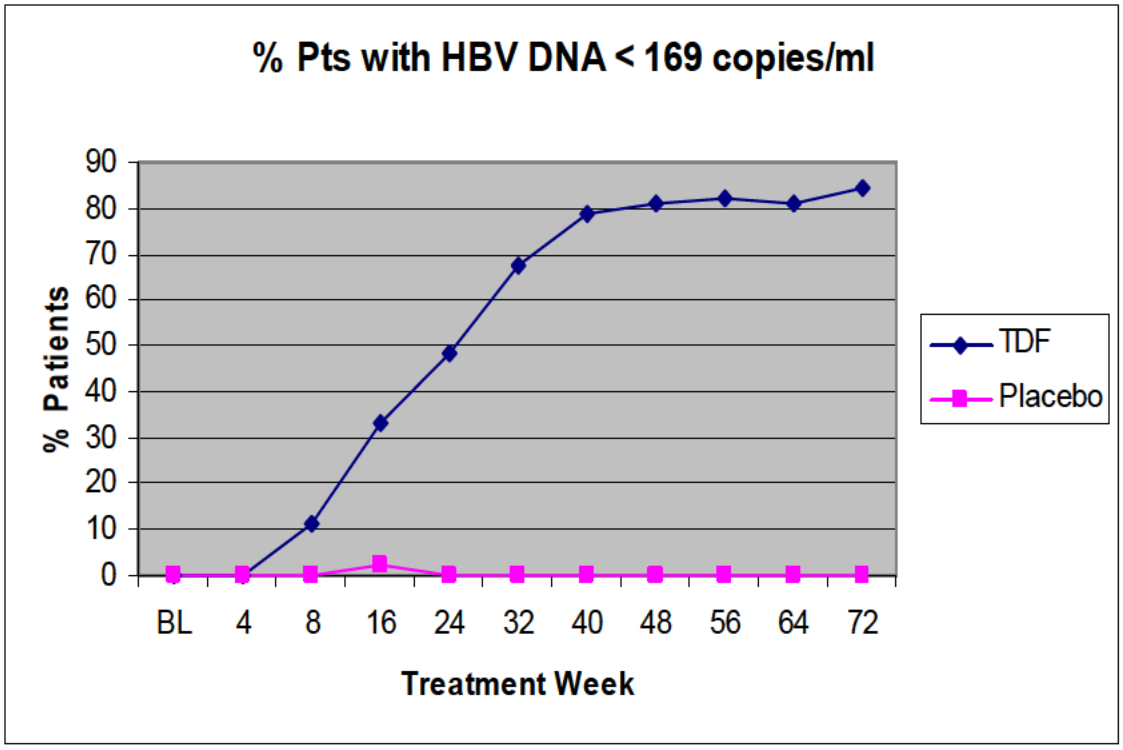
Percent of subjects with HBV DNA < 169 copies/ml:

169 copies/ml is the lower limit of quantitation (LLoQ) of the HBV PCR assay used in this study. From baseline through Week 48, the percentage of TDF subjects who had HBV DNA below the LLoQ rose sharply. Subjects were able to maintain this degree of viral suppression over time, and 84.6% of TDF-treated subjects had HBV DNA < 169 copies/ml at Week 72. As previously discussed with the primary efficacy endpoint, none of the placebo subjects attained this degree of viral suppression (84.6% TDF vs. 0% PLB, p <0.001). The data are presented in Table 9 and Figure 4.

Table 9: Percentage of Subjects with HBV DNA < 169 copies/ml

Study Week	TDF N=52	Placebo N=54
Baseline	0	0
4	0	0
8	11.5	0
16	33.3	2
24	48.1	0
32	67.3	0
40	78.8	0
48	80.8	0
56	82	0
64	80.8	0
72	84.6	0

Figure 4: Percent of Subjects with HBV DNA < 169 copies/ml over Time



Medical Officer Comment: HBV PCR < 169 copies/mL is considered an "undetectable" viral load, indicating excellent viral suppression. These data mirror those of the primary efficacy endpoint.

Percent of Subjects with Normal and Normalized ALT

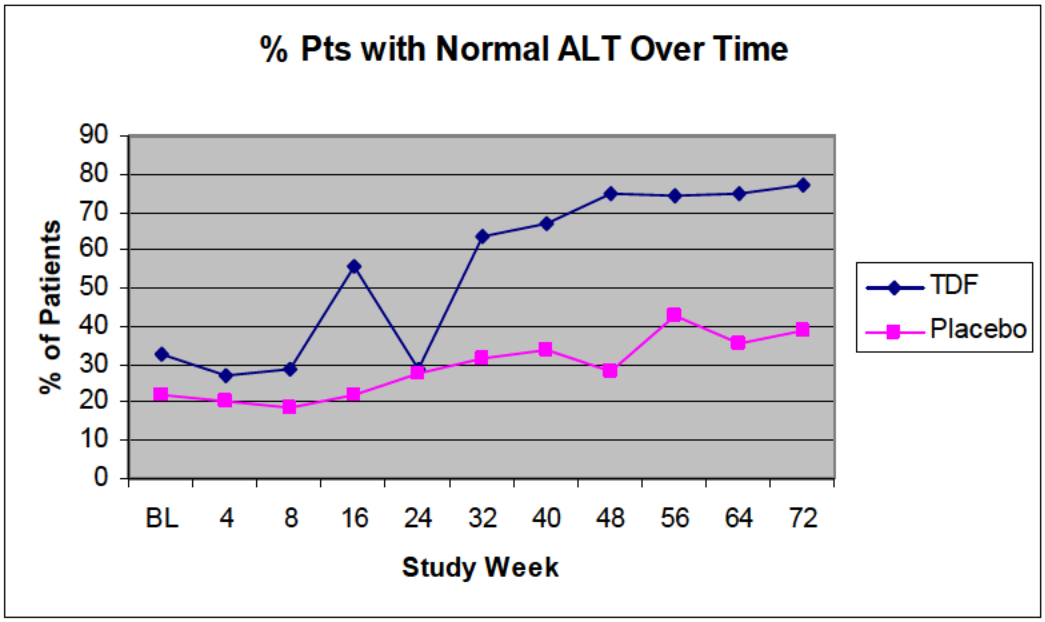
The Sponsor did several analyses regarding normalization of ALT. These included normalization of ALT among subjects with an abnormal ALT at baseline, as well as the percent of patient with normal ALT overall, regardless of the ALT value at study entry. There is no consensus regarding the upper limit of normal ALT for adolescents. The Sponsor acknowledges this, and used the values of 43 U/L for adolescent males and 34 U/L for adolescent females.

There was some imbalance between study groups at baseline, with a larger percentage of subjects with normal ALT in the TDF group than in the PLB group (32.7% versus 22.2%, respectively). At Week 72 the discrepancy between groups had widened and this difference was statistically significant (76.9% of subjects in the TDF group and 38.9% of subjects in the placebo group had a normal ALT at Week 72, $p < 0.001$). Therefore, despite the difference at baseline, a higher proportion of subjects in the TDF group who were abnormal at baseline had a normal ALT at the end of the study compared to subjects in the PLB group. Mean ALT change from baseline at Week 72 was -58 U/L (SD 121.1) in the TDF group and -13 U/L (SD 143.8) in the PLB group. The results are summarized in Table 10 and Figure 5.

Table 10: Percent of Subjects with Normal ALT by Study Week

Study Week	TDF N=52	Placebo N=54
Baseline	32.7	22.2
4	26.9	20.4
8	28.8	18.5
16	55.8	22.2
24	28.8	27.8
32	63.5	31.5
40	66.7	34
48	75	28.3
56	74	42.6
64	75	35.2
72	76.9	38.9

Figure 5: Percent of Subjects with Normal ALT – all Subjects



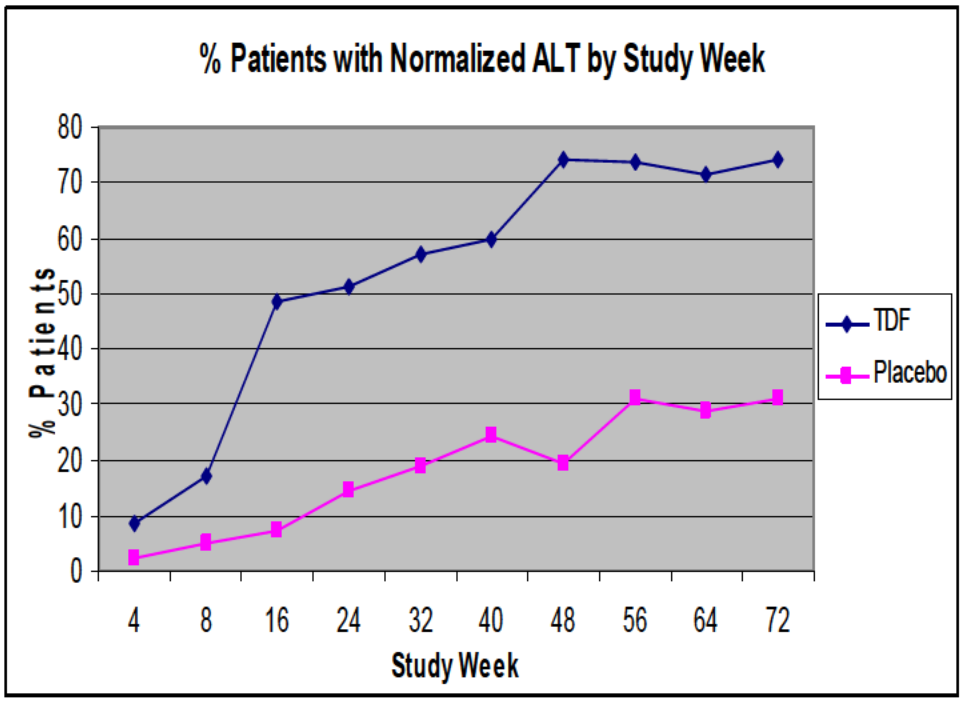
Medical Officer Comments: Among the TDF group, the increase in the proportion of subjects with normal ALT correlates with viral suppression, especially from Week 32 onward. The fluctuations from baseline among the PLB group are typical of chronic Hepatitis B infection in children.

Thirty-five TDF subjects (67%) and 42 PLB subjects (78%) had a baseline ALT greater than the upper limit of normal, as previously defined. Of those with elevated ALT, 74.3% of TDF subjects and 31% of PLB subjects had achieved a normal ALT by Week 72 ($p < 0.001$). These data are presented in the Table 11 and Figure 6.

Table 11: Percentage of Subjects with Baseline ALT > ULN with Normalized ALT by Study Week

Study Week	TDF N=35	Placebo N=42
4	8.6	2.4
8	17.1	4.8
16	48.6	7.1
24	51.4	14.3
32	57.1	19
40	60	24.4
48	74.3	19.5
56	73.5	31
64	71.4	28.6
72	74.3	31

Figure 6: Percent of Subjects with Normalized ALT by Study Week



Medical Officer Comment: These data mirror the findings of previous analyses, indicating that reduction of viral load correlates with decreased hepatic inflammation, as demonstrated by normalization of the ALT. Again, the rate of improvement is most pronounced early in the treatment course, and plateaus by Week 48.

HBV Serology

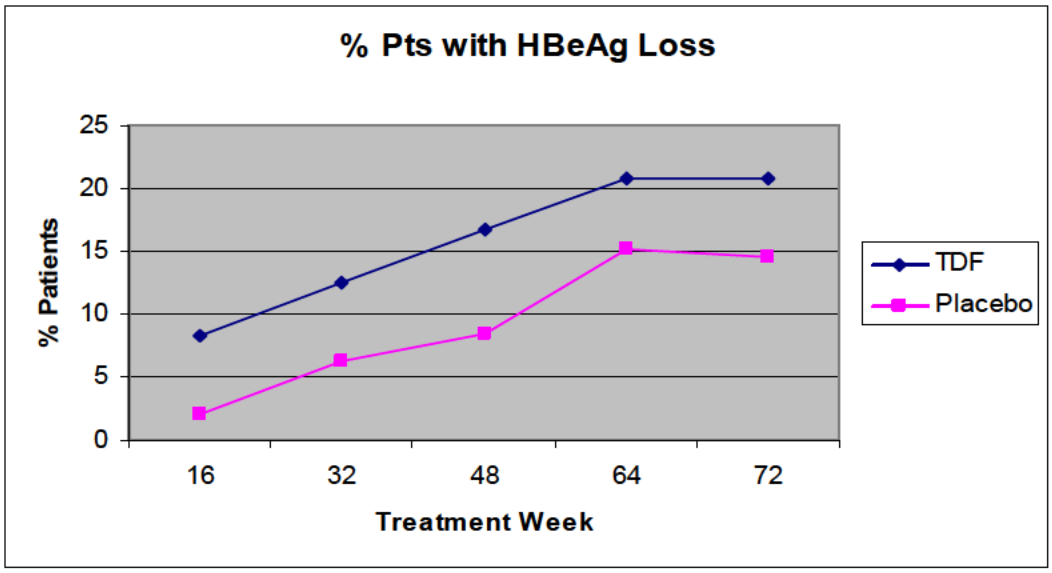
Subjects with Chronic Hepatitis B infection, by definition, are HBsAg positive and HBsAb negative. As such, all subjects were presumed to be HBsAg positive at study entry, though this parameter was not confirmed as part of study procedures. Both HBeAg positive and negative subjects were eligible to participate in the study. The majority were HBeAg positive at baseline, with 48 subjects each in the two study arms (48/52 for TDF and 48/54 for PLB).

Serologic evaluation was performed every 16 weeks, beginning with Week 16. Loss of the HBeAg at Week 72 was similar between the 2 treatment groups: 10 TDF (20.8%) and 7 PLB (14.6%), p=0.41. All subjects who had HBeAg loss also seroconverted to HBeAb positive. The data are presented in Table 12 and Figure 7.

Table 12: Percent of Subjects with HBeAg Loss by Study Week

Study Week	TDF	Placebo
16	8.3	2.1
32	12.5	6.3
48	16.7	8.5
64	20.8	15.2
72	20.8	14.6

Figure 7: Percent of Subjects with HBeAg Loss



Two subjects, both in the TDF group, experienced HBsAg loss during the first 72 weeks of study participation. Subject 1745-6002 had HBsAg loss and seroconversion to anti-HBsAb at Weeks 64 and 72. His baseline viral load was 49,993,800 copies/mL, and by Week 16 his HBV DNA was <169 copies/mL. He maintained this degree of viral suppression through Week 72, at which time his ALT was also within the normal range. Subject 3983-8003 had unconfirmed HBsAg loss at Week 32 with no seroconversion, and was HBsAg positive at subsequent visits though Week 72. This subject's viral load at Week 72 was < 169 copies/mL and ALT was within the normal range.

Medical Officer Comment: These results are similar to those from previous Hepatitis B studies using nucleotide/nucleoside analogues. Loss of HBeAg and seroconversion typically do not occur early in treatment. HBsAg loss and seroconversion occur even later, often requiring years of therapy. Therefore, the low rates of HBeAg and HBsAg loss and seroconversion should not be regarded as TDF failure.

6.1.6 Other Endpoints

The Sponsor performed a number of analyses of composite endpoints, some of which applied only to a subset of the total study population. As previously stated, all of the composite endpoints included the primary endpoint of HBV DNA < 400 copies/ml, and since the placebo group failed this endpoint, the group subsequently failed all composite secondary endpoints. These analyses will not be discussed in depth, but key results are summarized here.

1. For all subjects: composite endpoint of HBV DNA < 400 copies/mL and ALT normal. Thirty-seven of the 52 (71.2%) subjects in the TDF group and 0/54 subjects in the placebo group met this endpoint at Week 72. The difference between groups was statistically significant (p-value <0.001).
2. For HBeAg-positive subjects: 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: Forty-eight patients in each study arm were included in this analysis. A small proportion of TDF subjects, 7/48 (14.6%), met this composite endpoint at Week 72. No placebo subjects achieved this endpoint. The difference between groups remains statistically significant (p-value = 0.007).
3. For subjects with abnormal ALT at baseline: composite endpoint of HBV DNA < 400 copies/mL and ALT normalized. Thirty-five (67.3%) TDF patients and 54 (77.8%) PLB patients had an abnormal baseline ALT. At Week 72, 34/35 (97.1%) TDF patients and no PLB patients had HBV DNA < 400 copies/ml.

4. For HBeAg-positive subjects with abnormal ALT at baseline: 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. Thirty-three of 52 (63.4%) TDF subjects and 42/54 (77.8%) of TDF patients were HBeAg positive with an abnormal ALT at baseline. At Week 72, 7/33 TDF (21.2%) and no PLB patients met this endpoint (p-value = 0.002).

Medical Officer Comments: Since no placebo subjects met the primary efficacy endpoint of HBV DNA < 400 copies/mL, they also could not meet the composite endpoints. As such, analysis of these composite endpoints does not provide additional insight beyond that gained from analysis of the individual components (ie: ALT normalization, viral load reduction, seroconversion).

To put these results in historical context, the results from pediatric studies using adefovir and lamivudine were reviewed, keeping in mind that there are important differences in trial design that limit the comparisons. Both these studies were placebo controlled with a 2:1 ratio and included patients younger than 12. Only the oldest cohort was evaluated for the purpose of comparison with the TDF study. Each trial used a composite primary endpoint of Complete Virologic Response (CVR), though the definition of CVR differed between the two studies.

For adefovir, the primary efficacy endpoint was loss of HBeAg AND normalization of ALT at Week 48. Among the 12 to < 18 year-olds, 13/56 (23%) of adefovir subjects and no placebo subjects achieved CVR. Eleven percent of subjects in each treatment group had loss of HBeAg. For lamivudine, the primary efficacy endpoint was loss of HBeAg AND undetectable HBV DNA at Week 52. Among 13 to <18 year-olds, 8/47 (17%) of lamivudine subjects and 4/26 (15%) of placebo subjects achieved CVR.

The results from the adefovir and lamivudine trials are similar to the TDF results. However, comparisons of treatment effect are limited for many reasons, such as the use of different endpoints, including time of assessment.

6.1.7 Subpopulations

The small number of subjects enrolled in this study precludes meaningful analyses of subpopulations. In addition, substantial discrepancy in treatment effect between TDF and PLB subjects makes it difficult to delineate specific populations that are more or less successful when treated with tenofovir for hepatitis B.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. A single dose of 300mg by mouth daily was used in this study.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Subjects who received tenofovir and achieved an HBV DNA < 400 copies/ml were able to maintain viral suppression as long as they were treatment-adherent. All subjects enrolled in this study will be offered the opportunity to continue in the open-label phase of the study, which will monitor longitudinal treatment response.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Study GS-US-174-0115 demonstrated that TDF is a well-tolerated treatment for CHB in adolescents. The frequency of serious adverse events was relatively low. The safety issues identified in this study are similar to those previously described in adult and adolescent studies of HIV patients.

Decline in BMD is a well-known AE associated with TDF exposure in adults. Adolescence is a period of rapid growth, in which significant increases in BMD are expected. Overall, patients in both treatment groups gained BMD, but PLB patients gained more than TDF patients at each assessment. This trend is evident in several parameters (change in BMD, BMD Z-scores, biochemical markers of bone turnover) but clearly demonstrated by the percent change from baseline lumbar spine BMD: [Week 24 (TDF 1.9, PLB 3.4, p-value 0.005); Week 48 (TDF 3.5, PLB 5.6, p-value 0.046); Week 72 (TDF 5, PLB 8.1, p-value 0.053). It is unclear whether this difference has clinical implications. No patients met the primary safety endpoint of cumulative decrease ≥ 6% in lumbar spine BMD.

Renal toxicity is also a well-described complication of TDF therapy, but neither renal failure nor Fanconi's syndrome were observed in this study. Gastrointestinal side effects were also infrequently reported.

The safety review did not reveal new signals to monitor.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The results of GS-US-174-0115, a single double-blind placebo controlled clinical trial of TDF-naïve Hepatitis B infected adolescents, was reviewed to evaluate the safety of TDF. The Safety Analysis Set, which was used to perform the analyses in this review, included all randomized subjects who received at least one dose of study drug.

7.1.2 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary version 11.1. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.
The results of this study were evaluated in the context of the safety results from Study GS-US-104-0321, which enrolled HIV-infected adolescents. In addition, the safety evaluations of preceding phase 1 and 2 pediatric trials were reviewed. The data from these studies were used as a reference, and are not included in the safety analyses in this review.

7.2 Adequacy of Safety Assessments

TDF is an approved drug that is widely used in the US and abroad. As such, its safety profile is well established. The safety assessments conducted in this study were adequate to measure notable known toxicities (bone and renal) and to detect new signals.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 106 subjects (52 in the TDF group and 54 in the PLB group) were randomized and treated. All subjects completed at least 24 weeks of treatment, and 101 subjects (51 in the TDF group and 50 in the PLB group) completed the double-blind period through Week 72. Of the 4 subjects in the PLB group who did not complete the double-blind period, 2 entered the open-label period due to elevated ALT (per protocol) and 2 entered treatment- free follow-up after Week 72 without entering open-label period of the study, with the reason recorded as investigator's discretion. The one TDF patient who withdrew from study did so due to syncope (a condition that this patient had prior to study enrollment).

The mean duration of treatment was 497.3 days in the TDF group and 489.7 days in the PLB group. The percentage of subjects with 72 weeks of study drug exposure was > 92% in both groups.

7.2.2 Explorations for Dose Response

Dose response studies were not performed. All subjects received an identical dose of 300mg daily.

7.2.3 Special Animal and/or In Vitro Testing

No further nonclinical testing was performed in support of this application.

7.2.4 Routine Clinical Testing

Subjects were closely monitored through a combination of physical examination, anthropomorphic measurements, laboratory testing, and DEXA scanning. Please refer to Section 5.3, Table 3 for a full schedule of assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As previously stated, the side effect profile of TDF is well established, and the study was designed to evaluate all known toxicities.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during this study.

7.3.2 Nonfatal Serious Adverse Events

There were a total of 19 Serious Adverse Events (SAEs), of which 6 occurred in the TDF group and 13 occurred in the PLB group. Twelve of the 19 (63%) were hepatic events. The results are summarized in Table 13.

Table 13: Serious Adverse Events

SAE by SOC/*HLT*/ PT	**TDF** N=52 # cases (%)	**PLB** N=54 # cases (%)	**Total** N = 106 # cases (%)
Total Number of Subjects with SAE	6 (11.5%)	13 (24%)	19 (17%)
Hepatobiliary Disorders/ *Hepatocellular Damage and Hepatitis NOS*/ Hepatitis	2 (3.8%)	7 (13%)	9 (8.5%)
Investigations/ *Liver Function Analysis*/ Alanine Aminotransferase Increased	0	3 (5.6%)	3 (2.8%)
Renal and Urinary Disorders/ *Urinary Tract Signs and Symptoms NEC*/ Renal Colic	0	1 (1.9%)	1 (0.9%)
Injury, Poisoning, and Procedural Complications/ *Upper Limb Fractures and Dislocations/* Hand Fracture	1 (1.9%)	0	1 (0.9%)
Gastrointestinal Disorders/ *Gastrointestinal and Abdominal Pains*/ Abdominal Pain	0	1 (1.9%)	1 (0.9%)
Gastrointestinal Disorders/ *Gastritis*/ Gastroduodenitis	1 (1.9%)	0	1 (0.9%)
Infections and Infestations/ *Abdominal and Gastrointestinal Infections/* Appendicitis	1 (1.9%)	0	1 (0.9%)
Respiratory/Thoracic and Mediastinal Disorders/ *Bronchospasm and Obstruction*/ Asthma	0	1 (1.9%)	1 (0.9%)
Nervous System Disorders/ *Disturbances in Consciousness NEC/* Syncope	1 (1.9%)	0	1 (0.9%)

Medical Officer Comment: The majority of SAEs occurred in the PLB group and were a reflection of subjects' underlying CHB. The case narratives were reviewed for each of these subjects. All but 4 of the events were considered unrelated to study drug (see below). After reviewing the case narratives, this medical officer agrees that the events were unrelated to the study drug.

Decreased bone mineral density is known to be associated with TDF use, but has not been demonstrated to increase fracture risk. Special attention was given to the one TDF patient who sustained a hand fracture. His mechanism of injury was direct force after delivering a blow during an altercation. Fracture after such an act is not uncommon among healthy adolescents. As such, this reviewer considers the event unrelated to TDF. Other notable side effects with TDF include renal impairment (decreased Creatinine Clearance and Fanconi Syndrome) and gastrointestinal side effects (nausea, vomiting, diarrhea), but neither are reported as SAEs.

Four of the 19 SAEs were categorized as drug-associated SAEs. The patient narratives were reviewed for each case. One of the 4 subjects was randomized to TDF and reported hepatitis. The remaining three subjects were randomized to PLB, of which 2 had elevated ALT and 1 had abdominal pain.

Medical Officer Comment: Upon review of the patient narratives, it appears (based on the timing of events) that the drug-related hepatitis reported in one TDF recipient was related to loss of HBeAg. Therefore, it is the opinion of this clinical reviewer that the SAE was indeed drug-related, but that it is also heralded seroconversion, a marker of improved disease control.
The drug-related SAEs reported in the 3 PLB subjects are likely due to untreated CHB.

7.3.3 Dropouts and/or Discontinuations

A total of 3 subjects withdrew from the randomized phase of the study: one patient withdrew due to an SAE and the other two were transitioned early to open-label TDF.

The first patient (TDF) was a 16 year old male with a history of syncope who experienced Grade 4 syncope on study day 145. At the early termination visit, the subject's vital signs, cardiac examination, and respiratory examination were normal. The investigator deemed the event to be unrelated to study drug but the subject discontinued the study, with the reason cited as "investigator's discretion." An evaluation for cardiac arrhythmia was not undertaken.

The 2 remaining subjects had sustained Grade 4 elevations in ALT for greater than 16 weeks, which, according to the protocol, made them eligible for early transition to open-label TDF. Both subjects were randomized to PLB and switched to TDF at treatment week 40.

Medical Officer Comment: Overall, the study drugs were well-tolerated and the study had excellent subject retention. This clinical reviewer agrees that the TDF patient who withdrew for syncope was suffering from a condition unrelated to the study or study drug. However, the clinical reviewer disagrees with classifying the 2 early transition PLB subjects as discontinuations for SAEs. While it is true that sustained Grade 4 ALT

elevations are considered SAEs, the protocol called for early transition in these cases. Therefore, lack of efficacy, rather than concern for safety, was the motivation for early transition from the randomized study to open-label tenofovir.

7.3.4 Significant Adverse Events

Bone and renal toxicities are the primary safety concerns associated with tenofovir. Decreases in bone mineral density have been observed in adult HIV subjects receiving tenofovir. The effects tend to manifest early in treatment and then stabilize after 1-2 years of ongoing exposure. In pediatric studies, children have continued to gain bone mass (as expected during the years of rapid growth), but the gains they exhibited in bone mineral density have been less than that seen in controls.

The mechanism of this effect on bone is not clear, but there is suspicion that it relates to renal toxicity. The most commonly observed renal adverse events are increased creatinine clearance and Fanconi Syndrome (characterized by hypophosphatemia secondary to proximal renal tubular injury). The metabolic consequences of renal tubular injury, specifically hypophoshatemia, may affect bone metabolism and could be responsible for declines in bone density

Analyses of Bone Health
In the study currently under review, bone health was assessed with DEXA scanning to measure bone mineral density and measurement of biochemical markers of bone turnover.

Bone Mineral Density
Whole body and lumbar spine measurements were obtained by DEXA scanning at Weeks 24, 48, and 72. The data were analyzed using Z-scores and percent change from baseline for both the lumbar spine and the whole body.

Lumbar Spine
The primary safety endpoint was cumulative incidence of at least a 6% decrease from study baseline in lumbar spine BMD through Week 72. No subjects met this primary endpoint in either the TDF or placebo group, although one TDF patient came very close (5.9% decrease). Overall, subjects in the PLB arm gained more bone mineral density than those in the TDF group at each of the 3 assessments, conducted 24 weeks apart. Both groups exhibited net gains in BMD, as expected in childhood, but the TDF group lagged behind the placebo group. Statistically significant differences for mean lumbar spine BMD percent change from baseline were observed between the PLB and TDF groups at Week 24 and Week 48, and approached significance at Week 72. The results are summarized in Table 14.

Table 14: Change from Baseline Bone Mineral Density – Lumbar Spine

	TDF				Placebo			
	BL	**Week 24**	**Week 48**	**Week 72**	**BL**	**Week 24**	**Week 48**	**Week 72**
12-14 years	N=10	N=10	N=10	N=8	N=12	N=12	N=12	N=12
Mean BMD g/cm^2 (SD)	0.81 (0.1)	0.85 (0.1)	0.88 (0.1)	0.89 (0.1)	0.89 (0.1)	0.92 (0.1)	0.94 (0.2)	1 (0.1)
Min, Max	0.7,0.96	0.73, 0.97	0.76, 0.99	0.78, 0.99	0.59,1.08	0.64, 1.12	0.66, 1.15	0.75, 1.15
Mean % change from BL (SD)	N/A	4.4 (2.1)	9.3 (3.4)	11.8 (3.9)	N/A	6.1 (5.4)	9.1 (6.8)	14.1 (10.1)
Min, Max		1.5, 7.6	2.8, 14	3, 17		-3.8, 14.3	-2.3, 18.3	-2.7, 26.9
# (%) with increased BMD	N/A	10 (100)	10 (100)	8 (100)	N/A	10 (83)	10 (83)	11 (92)
# (%) with decreased BMD	N/A	0	0	0	N/A	2 (17)	2 (17)	1 (8)
# (%) with > 3% decrease in BMD	N/A	0	0	0	N/A	1 (8)	0	0
15-17 years	N=42	N=42	N=41	N=38	N=41	N=41	N=37	N=36
Mean BMD (SD)	1.05 (0.1)	1.06 (0.1)	1.07 (0.1)	1.09 (0.1)	1.04 (0.2)	1.07 (0.1)	1.09 (0.2)	1.1 (0.2)
Min, Max	0.7, 1.3	0.7, 1.3	0.7, 1.3	0.8, 1.3	0.8, 1.4	0.8, 1.3	0.8, 1.4	0.8, 1.4
Mean % change from BL (SD)	N/A	1.3 (3.4)	2.1 (3.6)	3.5 (4.7)	N/A	2.7 (2.9)	4.4 (4.9)	6.2 (6.1)
		-4.6, 11.9	-3.9, 11.1	-5.9, 15.5		-2.2, 11.1	-4, 18.6	-4.7, 21.7

Min, Max								
# (%) with increased BMD	N/A	28 (66.7)	27 (65.9)	31 (81.6)	N/A	33 (81.6)	30 (83)	31 (86.1)
# (%) with decreased BMD	N/A	14 (33.3)	14 (34.1)	8 (18.4)	N/A	8 (19.5)	7 (17)	5 (13.9)
# (%) with > 3% decrease in BMD	N/A	2 (4.9)	2 (4.9)	3 (7.9)	N/A	0	1 (2.4)	2 (4.9)
Total	N=52	N=52	N=51	N=47	N=53	n=53	N=49	N=48
Mean BMD (SD) Min, Max	1 (0.2) 0.7, 1.3	1.02 (0.2) 0.7, 1.3	1.03 (0.2) 0.7, 1.3	1.05 (0.2) 0.8, 1.3	1 (0.2) 0.6, 1.4	1.03 (0.2) 0.6, 1.4	1.05 (0.2) 0.7, 1.4	1.08 (0.2) 0.8, 1.4
Mean % change from BL (SD) Min, Max	N/A	1.9 (3.4) [-4.6, 11.9]	3.5 (4.5) [-3.9, 14]	5 (5.4) [-5.9, 17]	N/A	3.4 (3.8) [-3.8, 14.3]	5.55 (5.7) [-4, 18.6]	8.1 (8) [-4.7, 26.9]
p-value		0.005	0.046	0.053				
# (%) with increased BMD	N/A	38 (73.1)	37 (72.5)	39 (83)	N/A	43 (81.1)	40 (81.6)	42 (87.5)
# (%) with decreased BMD	N/A	14 (26.9)	14 (27.5)	8 (17)	N/A	10 (18.9)	9 (18.4)	6 (12.5)
# (%) with > 3% decrease in BMD	N/A	2 (3.8)	2 (3.9)	3 (6.4)	N/A	1 (1.9)	1 (2)	2 (4.2)

Medical Officer Comments: Adolescence is a period of rapid growth, and, as such, substantial gains in BMD are expected. The average expected growth in a healthy population would be around 15%. Both treatment groups are far below this expectation,

which suggests that chronic disease itself is adversely impacting bone health. The addition of TDF seems to further impair growth.

While the primary safety endpoint (cumulative decrease in BMD of 6% or more) was not met, one patient was extremely close with 5.9% decrease at Week 72. This patient entered the study with a low Z-score, likely a reflection of more severe CHB at baseline, and continued to have decreased bone growth relative to the remainder of the cohort.

Data from adult HIV studies suggest that the TDF effects are most prominent in the first 1-2 years of treatment and then stabilize. Long-term data in the pediatric population is not yet available, so it is unclear whether long term treatment in children will follow the same trend. It is theoretically possible that the "return to health" that will result from HBV suppression will lead to subsequent improvements in BMD gains that may offset the effects of TDF.

Change in Z-score was also analyzed to see how these children are growing in comparison to healthy children with the same demographic variables. Z-scores are established to compare an individual's BMD in relation to other individuals of the same age, sex, weight, and ethnic or racial origin. The score itself is the number of standard deviations above or below the mean, which is scored as 0. A score of -2 or lower is concerning for BMD that is significantly lower than the norm. Because the absolute values are small, the data in Table 15 represent the actual Z-scores at each assessment, rather than change from baseline (which was presented in the Table 14).

Table 15: Bone Mineral Density Z-score – Lumbar Spine

	TDF				Placebo			
	BL	**Week 24**	**Week 48**	**Week 72**	**BL**	**Week 24**	**Week 48**	**Week 72**
Age 12-14	n=10	N=10	N=10	N=8	N=12	N=13	N=13	N=12
Mean Z-score (SD)	-0.78 (0.5)	-0.79 (0.6)	-0.74 (0.6)	-0.7 (0.5)	-0.05 (0.8)	-0.03 (0.9)	-0.12 (0.9)	0.04 (0.7)
Min, Max	-1.4, 0.1	-1.52, 0.2	-1.69, 0.4	-1.22, 0.36	-1.69, 0.95	-1.5,1.1	-1.63, 1	-1.1, 1
# (%) with Z-score < -2	0	0	0	0	0	0	0	0
Age 15-17	N=42	N=42	N=41	N=39	N=41	N=41	N=37	N=36
Mean Z-score (SD)	-0.34 (0.8)	-0.41 (0.8)	-0.46 (0.8)	-0.38 (0.8)	-0.35 (0.8)	-0.33 (0.9)	-0.37 (0.9)	-0.3 (0.9)
Min, Max	-2.43, 0.83	-2.14, 0.87	-2.56, 0.78	-2.24, 0.86	-2.18, 1.21	-2.37, 1.2	-2.55, 1.2	-2.5, 1.3
# (%) with Z-score < -2	1 (2)	1 (2)	3 (7)	2 (5)	1 (2)	1 (2)	1 (2)	1 (2)
Total	N=52	N=52	N=51	N=47	N=53	n=54	N=50	N=48
Mean Z-score (SD)	-0.42 (0.8)	-0.5 (0.8)	-0.51 (0.8)	-0.43 (0.8)	-0.28 (0.8)	-0.26 (0.9)	-0.30 (0.9)	-0.22 (0.9)
Min, Max	-2.43, 0.83	-2.14, 0.87	-2.56, 0.78	-2.24, 0.86	-2.18, 1.21	-2.37, 1.2	-2.55, 1.2	-2.5, 1.3
# (%) with Z-score < -2	1 (2)	1 (2)	3 (6)	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)

Medical Officer Comments: Both groups begin with Z-scores below 0, indicating decreased bone maturity relative to age and sex-matched healthy children. In the placebo group, there is little variation in Z-score over the study period. In the TDF group, there seems to be some worsening during the first 48 weeks (consistent with what is seen in adults) and a trend toward baseline. It will be interesting to see which group has a higher mean score during the open label follow-up period.

Whole Body
Prior studies using TDF in HIV-infected subjects have demonstrated that the most notable declines in BMD were in the lumbar spine. Whole Body BMD data was also collected, and the absolute values, in addition to percent change from baseline, are summarized in Table 16.

Table 16: Change from Baseline Bone Mineral Density – Whole Body

	TDF				Placebo			
	BL	**Week 24**	**Week 48**	**Week 72**	**BL**	**Week 24**	**Week 48**	**Week 72**
12-14 years	N=9*	N=10	N=10	N=7	N=13	N=13	N=13	N=13
Mean BMD g/cm^2(SD) Min, Max	0.95 (0.04) 0.9, 1	0.98 (0.06) 0.9, 1.1	0.99 (0.07) 0.9, 1.1	1.02 (0.07) 0.9, 1.2	1 (0.08) 0.9, 1.2	1.03 (0.09) 0.9, 1.2	1.05 (0.09) 0.9, 1.3	1.08 (0.1) 0.9, 1.3
Mean % change from BL (SD) [Min, Max]	N/A	3.2 (2.5) -0.4, 6.9	5.1 (3.8) 0.7, 12.3	7.9 (3.7) 3.9, 14	N/A	3.4 (2.7) -0.24, 8.6	5.5 (3.5) 1.2, 14.6	8.4 (4.5) 3.3, 17.5
# (%) with increased BMD	N/A	8 (89)	9 (100)	6 (100)	N/A	12 (92.3)	13 (100)	13 (100)
# (%) with decreased BMD	N/A	1 (11)	0	0	N/A	1 (7.7)	0	0
# (%) with > 3% decrease in BMD	N/A	0	0	0	N/A	0	0	0

15-17 years	N=43	N=42	N=39	N=38	N=41	N=41	N=36	N=36
Mean BMD (SD) Min, Max	1.1 (0.1) 0.9, 1.5	1.13 (0.1) 0.9, 1.4	1.13 (0.1) 0.9, 1.5	1.14 (0.1) 1, 1.5	1.09 (0.9) 0.9, 1.3	1.1 (0.1) 0.9, 1.3	1.12 (0.1) 0.9, 1.3	1.13 (0.1) 0.9, 1.3
Mean % change from BL (SD) Min, Max	N/A	0.7 (1.6) -2.2, 4	1.3 (2) -3.2, 4.9	2 (2.7) -3, 7.4	N/A	2.2 (1.7) -2.1, 8	3.3 (2.9) -4.6, 10.6	4.3 (3.7) -3, 15.3
# (%) with increased BMD	N/A	26 (61.9)	29 (74.3)	29 (76.3)	N/A	40 (97.6)	33 (91.7)	31 (88.9)
# (%) with decreased BMD	N/A	16 (38.1)	10 (25.7)	9 (23.6)	N/A	1 (2.4)	3 (8.3)	4 (11.1)
# (%) with > 3% decrease in BMD	N/A	0	1 (2.4)	0	N/A		1 (2.4)	1 (2.4)
Total	N=51	N=52	N=49	N=45	N=54	N=54	N=49	N=49
Mean BMD (SD) Min, Max	1.09 (0.1) 0.9, 1.5	1.1 (0.1) 0.9, 1.4	1.11 (0.1) 0.9, 1.4	1.12 (0.1) 0.9, 1.5	1.07 (0.1) 0.9, 1.3	1.1 (0.1) 0.9, 1.3	1.1 (0.1) 0.9, 1.3	1.12 (0.1) 0.9, 1.3
Mean % change from BL (SD) Min, Max	N/A	1.1 (2) -2.2, 6.9	2 (2.8) -3.2, 12.3	2.9 (3.4) -3, 14	N/A	2.5 (2) -2.1, 8.6	3.9 (3.2) -4.6, 14.6	5.4 (4.3) -3, 17.5
p-value		<0.001	<0.001	0.013				
# (%) with increased BMD	N/A	34 (66.7)	38 (77.6)	35 (79.5)	N/A	52 (96.3)	46 (93.8)	45 (91.8)

# (%) with decreased BMD	N/A	17 (33.3)	10 (20.4)	9 (20.5)	N/A	2 (3.7)	3 (6.2)	4 (8.2)
# (%) with > 3% decrease in BMD	N/A	0	1 (1.9)	0	N/A	0	1 (2)	1 (2)

* Missing baseline value affects the "n" value for assessment of % subjects with higher or lower BMD at Weeks 24, 48, and 72

Medical Officer Comments: Assessment of whole body BMD reinforces the findings of lumbar spine measurements, but does not yield any new information. As seen in the lumbar spine data, there is a statistically significant difference between the TDF and PLB groups, again favoring growth in the PLB population. Also as expected, there are fewer accounts of severe (>3%) losses in BMD than in the lumbar spine assessment, though the small numbers make it difficult to identify true trends.

Table 17: Bone Mineral Density Z-score – Whole Body

	TDF				Placebo			
	BL	**Week 24**	**Week 48**	**Week 72**	**BL**	**Week 24**	**Week 48**	**Week 72**
Age 12-14	N=9	N=10	N=10	N=7	N=13	N=13	N=13	N=13
Mean Z-score (SD)	-0.66 (0.6)	-0.65 (0.7)	-0.65 (0.8)	-0.42 (0.6)	0.04 (0.9)	0.17 (1)	0.15 (0.9)	0.23 (1)
Min, Max	-2, 0.15	-2.13, 0.17	-2.57, 0.27	-1.24, 0.54	-1.32, 2.34	-1.13, 2.73	-0.9, 2.78	-1.08, 2.87
# (%) with Z-score < -2	1 (8)	1 (8)	1 (8)	0	0	0	0	0
Age 15-17	N=42	N=42	N=39	N=38	N=41	N=41	N=36	N=36
Mean Z-score (SD)	-0.1 (1.2)	-0.21 (1.1)	-0.37 (1)	-0.26 (1.1)	-0.35 (0.9)	-0.28 (0.9)	-0.39 (1.3)	-0.29 (1)
Min, Max	-2.72, 4.09	-2.88, 3.36	-3.13, 2.66	-2.06, 3.4	-2.61, 1.27	-2.91, 1.26	-2.98, 0.94	-2.94, 0.87
# (%) with Z-score <	2 (5)	3 (7)	3 (8)	2 (5)	1 (2)	1 (2)	1 (2)	1 (2)

-2								
Total	N=51	N=52	N=49	N=45	N=54	n=54	N=49	N=49
Mean Z-score (SD)	-0.2 (1.1)	-0.29 (1.1)	-0.43 (1)	-0.29 (1)	-0.26 (0.9)	-0.17 (0.9)	-0.24 (0.9)	-0.21 (1) 0.9
Min, Max	-2.72, 4.09	-2.88, 3.36	-3.13, 2.66	-2.06, 3.4	-2.61, 2.34	-2.91, 2.73	-2.98, 2.78	-2.94, 2.87
# (%) with Z-score < -2	3 (5)	4 (7)	4 (8)	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)

Medical Officer Comments: Following the trend of the lumbar spine data, the TDF subjects in both age cohorts reached their nadir at Week 48, with a trend back toward baseline at Week 72. The younger PLB cohort had consistent gains in BMD, while the older adolescents remained close to baseline.

Biochemical Markers of Bone Turnover (BTM)

BTMs can also be used to predict bone gain or loss. The majority of markers fall into one of two categories:

1) Proteins released by osteoclasts during bone resorption. These are primarily fragments of type 1 collagen, including N-telopeptide of type 1 collagen, C-telopeptide of type 1 collagen, deoxypyridinoline, and pyridinoline.
2) Proteins released by osteoblasts during bone formation. These may be proteins secreted by the osteoblasts or byproducts of type 1 collagen production, including bone specific alkaline phosphatase, osteocalcin, and P1NP [2].

In adults, elevations in bone specific alkaline phosphatase, osteocalcin, and deoxypyrinioline are among the most predictive markers of bone loss [3]. However, values can fluctuate over the course of a day, so ideally the tests should be obtained at the same time of day during longitudinal studies.

In this study, osteoblastic activity was gauged via measurement of bone specific alkaline phosphatase (BSAP) and osteocalcin, and osteoclastic activity was approximated via measurement of N and C telopeptides of collagen (C telopeptide is referred to as crosslaps). Vitamin D levels, calcium, phosphorus, and magnesium were also assessed. The results are summarized in Table 18.

Table 18: Mean Change from Baseline BTMs and Electrolytes

Treatment Week	TDF 12-14	TDF 15-18	TDF total	PLB 12-14	PLB 15-18	PLB total
Bone Specific Alkaline Phosphatase						
Baseline	101.7	48.1	57.8	110.5	42.6	58.9
Mean (SD)	(48.3)	(34.8)	(42.4)	(67.6)	(25.6)	(48.9)
N	(n=9)	(n=41)	(n=50)	(n=13)	(n=41)	(n=54)
24	73.8	37.2	44.8	82.7	30.8	44
Mean (SD)	(27.7)	(27)	(30.8)	(57.3)	(16.3)	(38.8)
N	(n=11)	(n=42)	(n=53)	(n=14)	(n=41)	(n=55)
48	70.1	31.8	39.4	78.6 (55)	27.9	41.1
Mean (SD)	(35.2)	(22)	(29.2)	(n=13)	(16.4)	(38)
N	(n=10)	(n=40)	(n=50)		(n=37)	(n=50)
72	51.5	27.4	32.1	73.2	24	36.8
Mean (SD)	(20.5)	(18.3)	(20.9)	(58.1)	(12)	(37.5)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=37)	(n=50)
Osteocalcin						
Baseline	146.8	74.2	88.4	120.8	79	89
Mean (SD)	(68.6)	(41.1)	(55.2)	(63.6)	(57.8)	(61.3)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=41)	(n=54)
24	119.5	63.5	75.3	93.1	63.1	70.3
Mean (SD)	(52.3)	(33.3)	(44.1)	(48.1)	(40.9)	(44.2)
N	(n=11)	(n=41)	(n=52)	(n=13)	(n=41)	(n=54
48	126	65.1	77	95.3	58.2	68
Mean (SD)	(61.3)	(38.2)	(49.4)	(55.1)	(35.2)	(44)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=36)	(n=49)
72	117.7	56.5	67.7	87.5	53.8	62.7
Mean (SD)	(56.8)	(29.2)	(42.4)	(45.2)	(28.8)	(36.7)
N	(n=9)	(n=40)	(n=49)	(n=13)	(n=36)	(n=49)
N-telopeptide						
Baseline	70.2	34.3	41.5	61.4	33.9	40.6
Mean (SD)	(27)	(23.7)	(28.1)	(29)	(24)	(27.8)
N	(n=10)	(n=40)	(n=50)	(n=13)	(n=40)	(n=53)
24	65.2	30.2	37.8	56	29.1	35.9
Mean (SD)	(25.4)	(17.9)	(24.3)	(27.8)	(17.6)	(23.5)
N	(n=11)	(n=40)	(n=51)	(n=13)	(n=39)	(n=52)
48	75.8	28.5	37.2	58	28.3	35.6

Mean (SD)	(49)	(18.2)	(31.8)	(30.5)	(16)	(23.9)
N	(n=9)	(n=40)	(n= 49)	(n=12)	(n=37)	(n=49)
72	57.8	24.2	30.6	39.5	26.2	29.9
Mean (SD)	(20.9)	(10.8)	(18.6)	(22.8)	(16.9)	(19.4)
N	(n=9)	(n=38)	(n=47)	(n=13)	(n=33)	(n=46)
C-telopeptide						
Baseline	2.5	1.6	1.8	2.2	1.6	1.7
Mean (SD)	(0.9)	(0.9)	(1)	(0.7)	(0.8)	(0.9)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=39)	(n=52)
24	2.2	1.4	1.6	1.9	1.2	1.4
Mean (SD)	(0.5)	(0.6)	(0.7)	(0.7)	(0.7)	(0.7)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=41)	(n=54)
48	2.6	1.4	1.6	2.1	1.4	1.6
Mean (SD)	(0.9)	(0.8)	(0.9)	(0.8)	(0.7)	(0.8)
N	(n=11)	(n=40)	(n=51)	(n=12)	(n=37)	(n=49)
72	2.5	1.3	1.5	1.8	1.3	1.4
Mean (SD)	(1)	(0.6)	(0.8)	(0.8)	(0.6)	(0.7)
N	(n=10)	(n=40)	(n=50)	(n=13)	(n=37)	(n=50)
Parathyroid Hormone						
Baseline	50	38	40.3	48.4	38.2	39.9
Mean (SD)	(28.2)	(20.9)	(22.7)	(26)	(21.2)	(22.4)
N	(n=10)	(n=42)	(n=52)	(n=13)	(n=41)	(n=54)
24	38	37.1	37.3	30.9	36.6	35
Mean (SD)	(17)	(12.9)	(13.7)	(11.8)	(17.7)	(16.3)
N	(n=11)	(n=41)	(n=52)	(n=14)	(n=37)	(n=51)
48	54.9	43.6	45.7	33	35.6	34.9
Mean (SD)	(24.5)	(16.7)	(18.6)	(13.9)	(17)	(16.1)
N	(n=9)	(n=40)	(n=49)	(n=13)	(n=35)	(n=48)
72	47.6	40.3	41.7	39.2	34.4	35.7
Mean (SD)	(22.5)	(17.8)	(18.8)	(24.3)	(15.6)	(18.2)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=36)	(n=49)
Vitamin D						
Baseline	18.8	20.8	20.4	18.9	21.7	21
Mean (SD)	(5.9)	(7.3)	(7)	(7.1)	(11)	(10.1)
N	(n=10)	(n=42)	(n=52)	(n=13)	(n=40)	(n=53)
24	25.5	25.8	25.8	23	23.7	23.5
Mean (SD)	(4.7)	(7.1)	(6.6)	(5.3)	(5.3)	(5.3)
N	(n=11)	(n=41)	(n=52)	(n=13)	(n=41)	(n=54)
48	22.7	24.2	24.1	21.7	22.9	22.5
Mean (SD)	(8.2)	(6.6)	(7.8)	(4.6)	(7.6)	(6.9)

N	(n=10)	(n=41)	(n=51)	(n=13)	(n=37)	(n=50)
72	25.3	26.4	26.2	22	26.2	25.1
Mean (SD)	(3.5)	(7.9)	(7.2)	(5.7)	(6.9)	(6.8)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=37)	(n=50)
Calcium						
Baseline	9.7	9.8	9.8	9.8	9.9	9.8
Mean (SD)	(0.5)	(0.3)	(0.3)	(0.4)	(0.3)	(0.3)
N	(n=10)	(n=43)	(n=53)	(n=13)	(n=40)	(n=53)
24	9.9	9.7	9.8	9.9	9.9	9.9
Mean (SD)	(0.2)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)
N	(n=10)	(n=42)	(n=52)	(n=20)	(n=52)	(n=72)
48	9.9	9.7	9.8	9.8	9.8	9.8
Mean (SD)	(0.3)	(0.3)	(0.3)	(0.2)	(0.3)	(0.3)
N	(n=10)	(n=43)	(n=53)	(n=16)	(n=37)	(n=53)
72	9.9	9.7	9.7	9.8	9.8	9.8
Mean (SD)	(0.2)	(0.3)	(0.3)	(0.2)	(0.3)	(0.3)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=37)	(n=50)
Phosphorus						
Baseline	4.8	4	4.1	4.7	3.9	4.1
Mean (SD)	(0.7)	(0.6)	(0.7)	(0.5)	(0.6)	(0.7)
N	(n=10)	(n=43)	(n=53)	(n=13)	(n=40)	(n=53)
24	4.7	3.9	4	4.3	3.8	3.9
Mean (SD)	(0.6)	(0.6)	(0.7)	(0.4)	(0.5)	(0.5)
N	(n=10)	(n=42)	(n=52)	(n=20)	(n=52)	(n=72)
48	4.5	3.8	4	4.2	3.8	3.9
Mean (SD)	(0.6)	(0.6)	(0.6)	(0.5)	(0.5)	(0.5)
N	(n=10)	(n=43)	(n=53)	(n=16)	(n=37)	(n=53)
72	4.5	3.8	3.69	4.2	3.7	3.9
Mean (SD)	(0.4)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)
N	(n=10)	(n=41)	(n=51)	(n=13)	(n=37)	(n=50)

Medical Officer Comments: Consultation has been requested from the Division of Reproductive and Urologic Products (DRUP) for assistance in interpretation of the BTMs and the BMD data as a whole. Dr. Stephen Voss, who has consulted on pediatric TDF studies in the past, has provided preliminary comments. He reports that the decline in BTMs observed in both study groups is normal for adolescence. This is the opposite trend from that seen in Study 0321 (adolescent HIV study), in which all markers increased. Dr. Voss postulates that this difference may be related to inherent differences between the 2 study populations related to their underlying disease, and that demographic differences may also be a factor (the CHB study population is mostly Caucasian, and the HIV study population is mostly Hispanic).

Looking at the overall BMD and BTM data, Dr. Voss's analyses are consistent with prior TDF studies which demonstrate a negative effect on bone metabolism. Since prior studies have not been placebo-controlled, this study provided an opportunity to evaluate the drug effect without the confounding effect of the HIV background drug regimen. The discrepancy in BMD gain between the TDF and control group seems more pronounced in the CHB population than in HIV studies. However, the clinical impact of the bone changes remains unclear. Analysis of long-term data from both study populations is necessary to determine whether the deleterious effects will wane with time or whether there will be cumulative loss, and whether these changes predispose patients to increased facture risk.

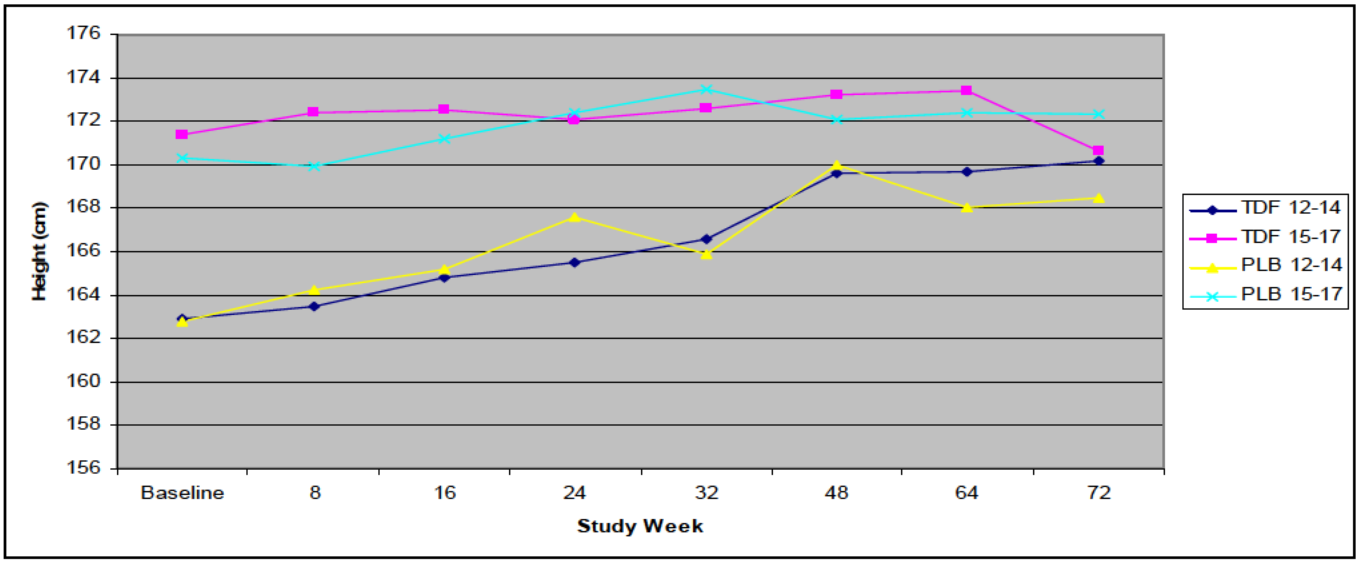
Please refer to Dr. Voss's review for further analyses and complete details.

Growth

Linear growth was assessed by examining both absolute changes in height and changes in height Z-score. The latter is a more useful comparison because it is standardized for age and sex. The limitation of such analysis, though, is that CDC data are used to create the Z-scores, which may not be fully applicable to the international population included in this study.

Figure 8 summarizes the mean measured height for each treatment group, stratified by age, over the course of the study.

Figure 8: Change in Linear Height by Study Group over Time



Medical Officer Comment: As expected, the 12-14 year old subjects in each treatment group had greater increases in growth than the 15-17 year old subjects of their respective treatment groups. Subjects followed roughly the same trajectory over time

irrespective of treatment assignment. The decreases in mean height are likely the result of errors in measurement.

Table 19 summarizes the mean *change* from baseline height Z-score at Weeks 24, 48, and 72. A z-score of 0 indicates that the individual is at the mean for age and sex. Negative scores are below the mean and positive scores are above the mean.

Table 19: Change in Height Z-score by Study Week

Study Week	TDF 12-14 years	TDF 15-17 years	Total TDF	PLB 12-14 years	PLB 15-17 years	Total PLB	p-value
Week 24							
N	10	42	52	13	41	54	
Mean (SD)	-0.30 (0.17)	-0.14 (0.31)	-0.17 (0.29)	-0.10 (0.25)	-0.02 (0.32)	-0.04 (0.30)	0.014
Week 48							
N	10	41	51	13	38	51	
Mean (SD)	-0.19 (0.21)	-0.15 (0.37)	-0.16 (0.34)	-0.02 (0.37)	-0.09 (0.35)	-0.07 (0.35)	0.093
Week 72							
N	10	41	51	13	37	50	
Mean (SD)	-0.49 (0.50)	-0.25 (0.41)	-0.30 (0.43)	-0.04 (0.46)	-0.12 (0.39)	-0.10 (0.41)	0.046

Medical Officer Comments: Both the TDF and PLB groups had Z-scores below the mean throughout the study period. However, the PLB group had mean scores closer to 0 (closer to the age and sex matched mean) than those in the TDF group, and the difference between groups achieved statistical significance at 2 of the 3 time points. The clinical relevance of these differences is unknown, but further longitudinal data from the open label study will be useful to determine whether TDF exposure has long-term implications on growth.

Renal Toxicity

Renal toxicity is well described among TDF recipients, and is thought to be due to proximal renal tubule injury. Manifestations include elevated creatinine, decreased calculated creatinine clearance, and hypophosphatemia. None of the subjects in either treatment group had a confirmed increase from the baseline serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. There were no cases of glycosuria or proteinuria. There were 10 cases of hematuria, all of which were in female subjects, which may be due to menstrual contamination.

Eight subjects (6 subjects in the TDF group and 2 subjects in the PLB group) had a confirmed increase in serum creatinine of 0.3 mg/dL (defined as 2 consecutive increases of 0.3 from baseline, or an increase of 0.3 from baseline for the last value in the double blind period). These elevations were not considered to be clinically significant and did not interrupt treatment or require dose adjustment. One TDF patient and 2 PLB subjects had unconfirmed cases of hypophosphatemia. Eight subjects (3 TDF and 5 PLB) had a calculated creatinine clearance rate < 80 mL/min (using either the Schwartz or Cockcroft-Gault calculation). Table 20 summarizes the mean serum creatinine, calculated creatinine clearance, and phosphorus results.

Table 20 : Assessments of Renal Toxicity

	Baseline TDF	**Week 72 TDF**	**Baseline Placebo**	**Week 72 Placebo**
Creatinine (mg/dL)				
N	52	51	54	50
Mean (SD)	0.7 (0.12)	0.8 (0.13)	0.7 (0.13)	0.8 (0.12)
Creatinine Clearance (ml/min/1.73m^2)				
N	52	44	54	43
Mean (SD)	157 (24.7)	137 (21.4)	159 (32.5)	148 (22.7)
Phosphorus (mg/dl)				
N	52	51	54	50
Mean (SD)	4.1 (0.71)	3.9 (0.62)	4.1 (0.69)	3.9 (0.63)

Medical Officer Comments: The incidence of renal adverse events was lower in this study compared to other TDF studies. This may be due to differences in the underlying infections (i.e., HIV vs. HBV) or to concomitant medications (i.e., background HIV regimen). In order to further understand the pathophysiology of the renal toxicity, and the potential relationship between renal and bone impairment, additional assessments are being obtained in the pediatric CHB study of subjects >2 to 12 years of age.

7.3.5 Submission Specific Primary Safety Concerns

The relative occurrence of hepatic flares was compared between study groups. Hepatic flares can be the consequence of exacerbations in HBV activity, or can occur in response to the inflammatory cascade that occurs during seroconversion.

For the purpose of this study, on-treatment ALT flare was defined as:

- Serum ALT > 2 × baseline and > 10 × ULN, with or without associated symptoms OR
- Confirmed ALT elevation (defined as 1-grade shift or 2 × previous value) associated with confirmed changes outside of the normal range in other laboratory parameters suggestive of worsening hepatic function (total bilirubin ≥ 2 mg/dL above baseline, abnormal PT ≥ 2 seconds or INR ≥ 0.5 over baseline, abnormal serum albumin ≥ 1 g/dL below baseline or elevated serum lactate levels [if available], defined as 2 × ULN per the AACTG guidelines).

Overall, 2 subjects (3.8%) receiving TDF and 10 subjects (18.5%) receiving PLB experienced on-treatment hepatic flares.

TDF: One of the 2 subjects was HBeAg positive at baseline and had a hepatic flare at Week 8. By Week 16 the ALT had normalized, and he was found to be HBeAg negative. The other patient had a flare at Week 72. Since the event occurred at the end of the randomized phase of study, data is not available to determine whether this led to loss of HBeAg.

PLB: Seven of the 10 subjects were HBeAg positive at baseline and all 7 remained positive through 72 weeks. Therefore these flares were not associated with seroconversion, and instead appear to be markers of ongoing liver damage. The remaining 3 exhibited sustained HBeAg loss at weeks 64, 32, and 48 respectively.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, treatment-emergent AEs were reported by 84.6% of subjects in the TDF group and in 88.9% of subjects in the PLB group. Grade 2−4 AEs were reported by 48.1% of subjects in the TDF group and 66.7% of subjects in the PLB group. Grade 3–4 AEs were reported in 9.6% of subjects in the TDF group and 24.1% of subjects in the PLB group. Serious adverse events were reported by 11.5% of subjects in the TDF group and 22.2% of subjects in the PLB group. Table 21 provides a summary of AEs.

Table 21: Overview of Treatment-Emergent Adverse Events

	TDF N=52	**Placebo N=54**
Total AEs	44 (85%)	48 (89%)
Grade 3 or 4	5 (10%)	13 (24%)
Drug Related AEs	8 (15%)	9 (17%)
Grade 3 or 4	1 (2%)	4 (8%)
AE causing dose change /interruption of study medication	0	1 (2%)

The most frequently reported treatment-emergent AEs reported in ≥ 20% of subjects in either treatment group were pharyngitis (28.8% in the TDF group and 20.4% in the PLB group), nasopharyngitis (9.6% in the TDF group and 22.2% in the PLB group), and increased ALT (5.8% in the TDF group and 22.2% in the PLB group). For those treatment-emergent AEs occurring with ≥ 5% incidence in either treatment group, statistically significant differences were noted only for increased ALT (p = 0.024), acne (p = 0.029) and lymphadenopathy (p = 0.027), all of which were of higher incidence in the PLB group than in the TDF group.

Table 22 summarizes treatment-emergent AEs of interest, either because they are known side effects included in labeling, or serious events that require scrutiny. Common AEs that are not considered adverse drug reactions, such as nasopharyngitis and acne, have been excluded. Events deemed as study-drug related are listed in the columns on the right, and represent a subset of the total events included in the columns on the left.

Table 22: Selected Treatment-Emergent AEs Occurring in >5% of Study Population

	All Events		Study-Drug Related Events	
AE n (%)	**TDF N=52**	**PLB N=54**	**TDF N=52**	**PLB N=54**
Hepatic				
ALT increased	3 (6%)	12 (22%)	1 (2%)	4 (7%)
AST increased	0	3 (6%)	0	0
Lipase increased	2 (4%)	1 (2%)	0	0
Malaise	1 (2%)	2 (4%)	0	1 (2%)
Gastrointestinal				
Abdominal Pain	3 (6%)	7 (13%)	1 (2%)	1 (2%)
Diarrhea	4 (8%)	1 (2%)	0	0
Vomiting	0	3 (6%)	0	1(2%)
Nausea	2 (4%)	2 (4%)	2 (4%)	0
Anorexia	1 (2%)	2 (4%)	0	1 (2%)
Gastritis	0	2 (4%)	0	0
Bone Pain	0	2 (4%)	0	1(2%)
Cardiac rate/rhythm	0	2 (4%)	0	0

Table 23 highlights the more severe treatment emergent AE's, designated by the investigators as Grade 3 or 4. Again, events deemed as study-drug related are listed in the columns on the right, and represent a subset of the total events included in the columns on the left.

Table 23: Grade 3 or 4 Treatment Emergent AEs

	All Events		Study-Drug Related Events	
AE (n/%)	**TDF N=52**	**PLB N=54**	**TDF N=52**	**PLB N=54**
Hepatic				
ALT increased	0	5 (10%)	0	3(6%)
AST increased	0	1 (2%)	0	0
Hepatitis	2 (4%)	6 (11%)	1 (2%)	0
GI				
Abd Pain	0	1 (2%)	0	1 (2%)
Flatulence	0	1 (2%)	0	0
Vomiting	1	1 (2%)	0	1 (2%)
Renal Colic	0	1 (2%)	0	0
Fracture (hand)	1 (2%)	0	0	0

Medical Officer Comments: AEs common to childhood and adolescence, including the most frequent in this trial (nasopharyngitis, pharyngitis, acne) will not be discussed here, as there is no biologically plausible relationship between the drug, CHB, and these conditions.

Hepatic AEs were reported more frequently in the PLB group. Other GI AEs that are reported more frequently in the PLB arm, such as abdominal pain and vomiting, may be related to untreated CHB. Diarrhea and nausea/vomiting are frequently observed among adults taking TDF, but were not frequently reported in this small study.

Bone and renal events have already been discussed (see Section 7.3.4). The case of renal colic seen in the placebo group occurred in girl with a non-functional kidney who ultimately required nephrectomy. No similar events occurred in the TDF arm. Additional safety signals (including but not limited to neurologic, cardiac, or hematologic derangements), were not observed.

7.4.2 Laboratory Findings

Subjects in this study underwent close laboratory evaluation, including CBC, comprehensive metabolic panel, and urinalysis. Hematologic parameters and electrolytes were stable for both treatment groups. PT decreased modestly in both groups. The most marked discrepancy between groups was in transaminase elevation, which was much more common in the PLB group. Table 24 summarizes the Grade 3 and 4 laboratory abnormalities.

Table 24: Grade 3 and 4 Lab Abnormalities

	TDF (n=52)	PLB (n=54)
Total Number of Subjects (%)	14 (26.9)	27 (50)
Chemistry		
Creatinine Kinase	1 (1.9)	1 (1.9)
Amylase	2 (3.8)	1 (1.9)
Lipase	3 (5.8)	1 (1.9)
Hepatic		
ALT	6 (11.5)	22 (40.7)
AST	3 (5.8)	9 (16.7)
Urinalysis		
Hematuria	4 (7.7)	6 (11.1)

Medical Officer Comments: The PLB group had more grade 3 or 4 laboratory abnormalities than the TDF group, of which the majority were ALT elevation. This is consistent with untreated Hepatitis B in the PLB group. These data suggest that the study population had significant hepatic inflammation and, as such, represents an appropriate population to treat.

Of note in the TDF group are the subjects with elevated amylase and lipase. Grade 3 or 4 elevations in amylase/lipase were not seen In the TDF trial of HIV-1-infected adolescents, but were seen among the 2-12 year old cohort in similar numbers. Because of the small number of subjects in each of these studies, it is difficult confirm causality.

Also notable is the lack of neutropenia seen in these subjects, which is a labeled adverse event associated with TDF.

All 10 subjects with hematuria were female, which raises suspicion for menstrual contamination. No Grade 3 or 4 elevations in creatinine were observed.

7.4.3 Vital Signs

Vitals signs were measured at each study visit, and there were no remarkable abnormalities in either study arm.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained in this study.

7.4.5 Special Safety Studies/Clinical Trials

The only special studies were DEXA scans, discussed previously in Section 7.3.5.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable, as only a single dose was studied.

7.5.2 Time Dependency for Adverse Events

Decreases in BMD seemed to peak at 48 weeks into treatment, but since there was only one subsequent evaluation, long-term data is required for confirmation.

7.5.3 Drug-Demographic Interactions

The small number of subjects, in conjunction with a small number of AEs, precludes meaningful analysis of demographic characteristics.

7.5.4 Drug-Disease Interactions

Adherence to the treatment regimen results in profound viral suppression in the majority of subjects. Non-responders often did not take their medications, as demonstrated by low PK levels.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not formally studied in this trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies during the study. Only 31% of the study population was female.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please see section 7.3.5 for discussion regarding effects on bone mineral density and linear growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

TDF has been commercially available since 2001 for treatment of HIV-1 and since 2008 for HBV in adults. It is marketed both individually as Viread®, and as part of fixed-dose combinations, including Truvada, ® Atripla®, and Complera®. TDF was approved for pediatric use in HIV-1 infected adolescents in 2010, and in accordance with the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Childrens Act (BPCA), a post-marketing safety review was conducted one to two years following pediatric approval. The results of this inquiry were presented to the Pediatric Advisory Committee on May 7, 2012. The pertinent findings are summarized here.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from the time of approval (October 26, 2001) up to January 9, 2012. AERS contained 9,230 reports for tenofovir, of which 427 (4.6%) were pediatric reports. There were 5 deaths, none of which represented an unexpected toxicity due to tenofovir. Four of the 5 patients were infants enrolled in a clinical trial who died of medical issues unrelated to antiretroviral therapy. The fifth child died of lactic acidosis associated with exposure to NRTIs, which is a boxed warning.

Commonly reported non-fatal event outcomes included renal dysfunction (N=19) and decrease in bone mineral density (N=6), both of which are labeled in Warnings and Precautions. Other reported events of interest included anemia (N=6, all were confounded by use of zidovudine which is labeled for anemia), cardiac events (N=2, one case was confounded by Coxsackie B6 virus and the other case had insufficient clinical information to assess), and bone marrow necrosis with decrease in the white blood cell

count (N=1, confounded by use of didanosine which is labeled for anemia, leukopenia, and thrombocytopenia).

9 Appendices

9.1 Literature Review/References

1) Section 11 of the Viread Product Label, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021356s038lbl.pdf. Last accessed on June 29, 2012.

2) Lewiecki EM. Benefits and limitations of bone mineral density and bone turnover makers to monitor patients treated for osteoporosis. Curr Osteoporos Rep 2010, 8(1):15-22.

3) Ross PD, Knowlton W. Rapid bone loss is associated with increased levels of biochemical markers. J Bone Miner Res 1998,13(2):297-302.

9.2 Labeling Recommendations

Section 1.2 (CHB indication) will be updated to include pediatric patients 12 years of age and older. Section 2 will be edited to harmonize dosing instructions for adolescents. BMD data will be included in Section 5.6. Section 6.1 will be updated with general safety data, and a description of the trial will be added to Section 8.4. Labeling discussions were ongoing at the time this review was completed, therefore the details are yet to be finalized.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA application.

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/s/

PRABHA VISWANATHAN
07/24/2012

LINDA L LEWIS
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