OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA(s)	**21356/S-42 (tablet); 22577/S-02 (oral powder)**
Submission Date	**February 16, 2012**
Brand Name	**VIREAD®**
Generic Name	**Tenofovir disoproxil fumarate**
Reviewer	**Dionna Green, M.D.**
Team Leader (acting)	**Shirley Seo, Ph.D.**
OCP Division	**DCP IV**
OND Division	**DAVP**
Sponsor	**Gilead Sciences Inc.**
Relevant IND(s)	**52,849**
Submission Type; Code	**Pediatric efficacy supplement**
Review Type(s)	**Priority**
Currently Marketed Formulation(s)	**Tablet (300-, 250-, 200-, and 150 mg); Oral powder (40 mg/1gm)**
Approved Indication(s)	**Treatment of chronic hepatitis B infection in adults; Treatment of HIV-1 in combination with other antiretroviral agents in adults and children 2 years of age and older**
Approved Dosing Regimen(s)	**Adults: 300 mg once daily without regard to food** **Peds.: 8 mg/kg once daily (up to a max. of 300 mg) without regard to food**
Proposed Dosing Regimen	**300 mg once daily without regard to food**
Proposed Indication	**Treatment of chronic hepatitis B infection in pediatric patients 12 years of age and older**

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1 EXECUTIVE SUMMARY

Tenofovir disoproxil fumarate (TDF, VIREAD®) is the prodrug of tenofovir, a human immunodeficiency virus-1 (HIV-1) nucleotide reverse transcriptase inhibitor and hepatitis B virus (HBV) polymerase inhibitor indicated for the treatment of HIV-1 (in combination with other antiretroviral agents) in patients 2 years of age and older as well as for the treatment of chronic hepatitis B in adults. The recommended dosing regimen for the treatment of HIV-1 in adults and adolescents and for the treatment of chronic hepatitis B in adults is TDF 300 mg once daily taken orally. In this current submission, the Applicant is seeking to extend the adult dosing regimen to HBV-infected pediatric patients 12 to <18 years of age and weighing at least 35 kg based on one safety and efficacy study (GS-US-174-0115).

In addition, this submission contains proposed revisions to sections 7.1 (Drug Interactions) and 12.3 (Assessment of Drug Interactions) of the TDF package insert based upon the outcome of audits and validation of data from clinical pharmacology studies conducted by (b) (4) in support of the original approval.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted in this efficacy supplement and agrees that it supports the proposal to extend the adult dosing regimen (TDF 300

mg once daily) to patients 12 to <18 years of age and weighing at least 35 kg for the treatment of chronic hepatitis B infection. Edits to the proposed label are recommended (See Section 3 Detailed Labeling Recommendations).

1.2 Phase IV Commitments

None

1.3 Summary of Key Clinical Pharmacology and Biopharmaceutics Findings

TDF is approved for the treatment of HIV-1 in adults and pediatrics 2 years of age and older and for the treatment of chronic hepatitis B in adults only. TDF 300 mg once daily taken orally is the recommended dosing regimen for the treatment of HIV in adults and adolescent patients and for the treatment of HBV infection in adults. The Applicant is proposing to extend this dosing regimen to HBV infected adolescents 12 to <18 years of age who weigh at least 35 kg using the marketed TDF 300 mg tablet.

One randomized, double-blind safety and efficacy study in adolescents (12-17 years old) with chronic hepatitis B infection was completed in support of this efficacy supplement (GS-US-174-0115). In Study 0115, 106 subjects were randomized to receive either TDF 300 mg/day or placebo (1:1 ratio). Randomization was stratified by age group (12-14 years and 15-17 years) and by geographic location (North America and Europe). The primary efficacy endpoint was the proportion of subjects with HBV DNA <400 copies/mL at Week 72. At the start of treatment, all subjects had a HBV DNA count of $\geq 10^5$ copies/mL. At Week 72, 88.5% of TDF-treated subjects achieved the primary endpoint as compared to 0% of the placebo-treated subjects. Six out of the 52 TDF-treated subjects were classified as virologic failures (HBV DNA >400 copies/mL at Week 72).

A sparse sampling scheme was utilized to assess tenofovir pharmacokinetics in Study 0115. One randomly-timed plasma sample was collected from all subjects at each study visit. Pooled tenofovir plasma concentrations overall and by age group at study baseline were used for the pharmacokinetic analysis **(Table 1)**. Mean tenofovir exposures in this study were comparable to historical data from HIV-infected adolescents (GS-US-104-0321, GS-01-926, and GS-01-927) and adults (GS-97-901 and GS-99-907), as well as from healthy adults **(Table 2)**. Thus, the pharmacokinetic data supports the appropriateness of the TDF 300 mg once daily dosing regimen for HBV infected adolescent patients.

Table 1 – Mean and Median Tenofovir Pharmacokinetic Parameters Calculated from Pooled Concentration Data Overall and By Age Group

Age Category	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	T_{max} (h)
Overall				
Mean	3015.2	352.7	19.2	1.5
Median	2884.1	341.0	19.9	1.5
15 – < 18 years				
Mean	2904.6	306.6	15.4	1.5
Median	2813.2	370.0	19.5	0.25
12 – 14 years				
Mean	-	444.7	-	1.5
Median	-	480.0	-	1.5

Table 2 – Tenofovir Pharmacokinetic Parameters Following Multiple Doses of TDF 300 mg/day in HBV Infected Adolescents, and Comparative Historical Data in HIV-1 Infected Adolescents and Adults

TFV Steady-state PK Parameter	GS-US-174-0115 300 mg/day (N=52)[a]	Historical Data in HIV-1 Infected Adolescents		Historical Adult Data in HIV-1 Infected Adults					
		GS-US-104-0321 300 mg/day (N=8)[b]	GS-01-926 and GS-01-927 300 mg/day (N=7)[b]	GS-97-901 300 mg/day		GS-99-907 300 mg/day			
				8th Dose (N=8)	28th Dose (N=8)	12 Weeks (N=12)	24 Weeks (N=12)	36 Weeks (N=7)	48 Weeks (N=7)
AUC_{tau} (ng•h/mL)[c] Mean (%CV)	3015.2	3390.6 (36.0)	3007.8 (27.8)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	352.7	377.5 (35.6)	268.3 (27.2)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL)[c] Mean (%CV)	—	64.4 (52.6)	63.0 (36.4)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.5	1.98 (1.46, 2.99)	2.08 (1.00, 4.00)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h)[c] Median (Q1, Q3)	19.9	10.54 (9.02, 15.30)	13.99 (7.97, 17.30)	13.7	14.4	14.0	14.9	12.4	14.5

NDA 21356/S42 also includes the Applicant's proposed labeling revisions to sections 7.1 (Drug Interactions) and 12.3 (Assessment of Drug Interactions) of the TDF package insert.

These revisions include streamlining and clarification of language in these labeling sections, as well as revisions pertaining to the removal of (b) (4) These proposed changes to the labeling were originally submitted to the Agency October 12, 2010 (NDA 21356/S35 SDN 502).

(b) (4)

For study 932, a follow-up and more relevant study was subsequently conducted using the 250 mg dose (the recommended dose of didanosine when given in combination with TDF) and the enteric-coated capsule formulation of didanosine. This study did not involve (b) (4) . Because of this, it was deemed by the Agency that the Applicant can (b) (4) The Applicant is proposing to (b) (4) the results for the 250 mg didanosine enteric-coated capsules in the USPI for Videx EC.

In addition, the Applicant is proposing to remove (b) (4) The changes proposed by the Applicant are acceptable.

2 QUESTION-BASED REVIEW

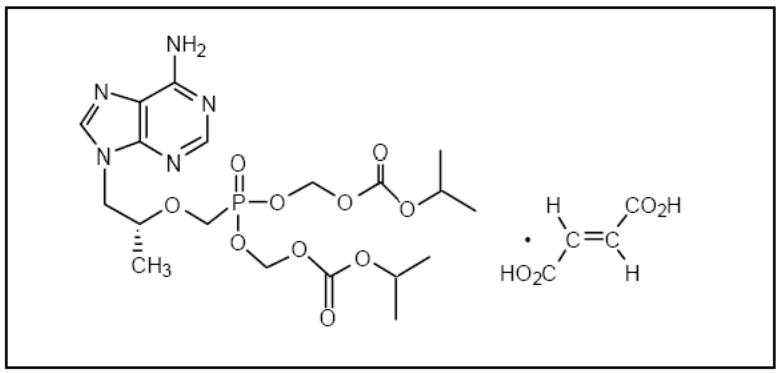
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Tenofovir disoproxil fumarate is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. TDF is commercially available as 150-, 200-, 250-, and 300 mg strength tablets or as an oral powder formulation.

Chemical name: 9-[2-(R)-[[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinoyl] methoxy]propyl]adenine fumarate

Structure:



Molecular formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$
Molecular weight: 635.52
Formulation: tablets, oral powder
Composition: TDF 150-, 200-, 250-, and 300 mg strength tablets

Component	Unit Formula					
	mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	%w/w
(b) (4) Tablet						
Tenofovir Disoproxil Fumarate[a]	150.0	200.0	250.0	300.0	300.0	45.0
Pregelatinized Starch	(b) (4)					
Croscarmellose Sodium[b]						
Lactose Monohydrate[a]						
Microcrystalline Cellulose[b]						
Magnesium Stearate						
(b) (4)						
(b) (4) Tablet Weight						
Film Coating Components						
Opadry II Blue Y-30-10671-A[d]	(b) (4)					
Opadry II White 32K18425[e]						
(b) (4)						
Total Tablet Weight	346.6	462.2	577.8	693.4	693.4	-

NA = not applicable
a (b) (4)
b
c
d
e
f

Composition: TDF oral powder (40mg/1gm)

Component	Amount per Bottle (g/bottle)
Tenofovir DF[a]	2.4[b]
Mannitol	(b) (4)
Hydoxypropyl Cellulose	
Ethylcellulose	
Silicon Dioxide	

a (b) (4)

b

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

TDF is an oral prodrug of tenofovir. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, the active moiety. Tenofovir is a nucleotide analogue reverse transcriptase inhibitor and a HBV polymerase inhibitor which inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

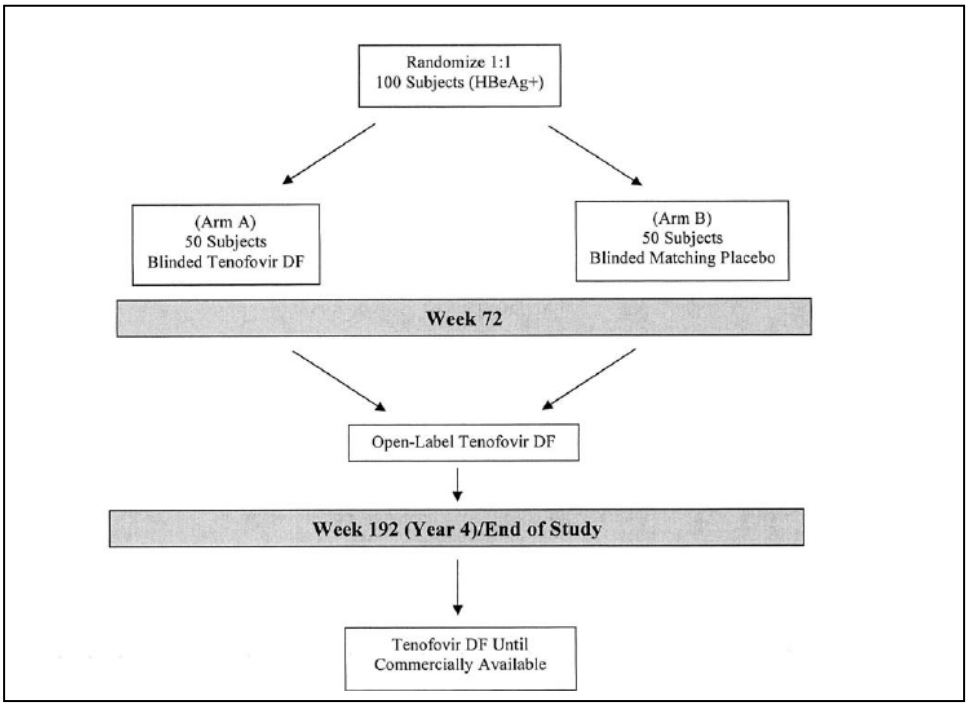
The proposed dosage regimen of TDF for the treatment of HBV infection in adolescent patients 12 to 17 years of age and weighing at least 35 kg is 300 mg taken orally once daily without regard to food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The study used to support dosing in adolescents was a Phase 3, 72-week, randomized, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of TDF 300 mg/day compared to placebo for the treatment of chronic hepatitis B infection in HBeAg positive or negative, TDF-naïve 12 to 17 year old subjects (GS-US-174-0015). The primary endpoint was the proportion of subjects achieving HBV DNA <400 copies/mL at Week 72. A total of 100 evaluable subjects were planned for this study. Sparse sampling in all subjects was performed to assess tenofovir pharmacokinetics. Following the randomized treatment period, eligible subjects entered into a currently ongoing, 120-week, open-label TDF extension study to evaluate the long-term safety and efficacy of TDF treatment. The schema for Study 0015 is depicted in the figure below:

GS-US-174-0015 Study Schema



2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints for TDF used for the basis of the original NDA approval in 2008 for the indication of treatment of chronic hepatitis B infection in adults included a complete response, defined as HBV DNA <400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points, without worsening in Knodell fibrosis at Week 48.

In Study 0115 in adolescent subjects 12 to <18 years of age, the primary endpoint was the proportion of subjects with HBV DNA <400 copies/mL at Week 72. Secondary endpoints measured at Weeks 48 and 72 included: ALT normalization; composite of HBV DNA <400 copies/mL and ALT normalization; HBV DNA <169 copies/mL; and HBsAg loss and seroconversion.

HBV DNA viral load is an accepted marker for determining treatment response.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

Yes, tenofovir was measured in plasma. TDF is converted to tenofovir *in vivo*. Tenofovir is subsequently phosphorylated intracellularly to its active moiety, tenofovir diphosphate. Therefore, the measurement of tenofovir in plasma, which serves as a surrogate for its intracellular form, is appropriate for assessing pharmacokinetic parameters.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

TDF 300 mg has been demonstrated to be the optimal dose of TDF for the treatment of HIV-1 infection. In the original NDA submission for the HIV-1 indication, formal PK/PD studies in adults to evaluate exposure-response were not performed. However, two studies conducted in HIV-1 infected adults (GS-97-901 and GS-97-902) appeared to support a dose-response relationship favoring the 300 mg once daily approved dosing regimen. Study 901 was a short-term dose ranging study which demonstrated initial decreases in HIV-1 RNA were greater in the 300-mg dose treatment group as compared to the 75-mg and 150-mg treatment groups over 21 days. Further reductions in HIV-1 viral load were not seen for the 600-mg treatment group. Study 902, also demonstrated that reductions in HIV-1 RNA were greater for the 300-mg group compared to the 75-mg and 150-mg groups over 48 weeks of treatment. A 600-mg dose was not evaluated in this study.

TDF 300 mg was selected as the dose to be evaluated in adult studies of chronic hepatitis B because the safety profile has been well characterized in the HIV-1 population with and without co-infection of chronic hepatitis B and is not significantly different from lower doses of TDF (75 mg and 150 mg). In addition, the inhibition constant (K_i) of tenofovir against HIV-1 reverse transcriptase is similar to the K_i against HBV polymerase. The effectiveness of the TDF 300 mg dose in HBV infected adults has been confirmed in Phase 3 studies (GS-US-174-0102 and GS-US174-0103).

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

An exposure-response relationship for safety has not been identified for TDF. The two main safety concerns for TDF are renal toxicity and bone toxicity, including decreases in bone mineral density.

2.2.4.3 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dosing regimen proposed for adolescents 12 to <18 years of age is supported by PK and efficacy data in HIV-1 infected adults and adolescents and by efficacy data in HBV infected adults. There are no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of tenofovir?

Tenofovir displays linear PK and dose-proportional increases in exposures across doses ranging from 75 to 600 mg. Tenofovir exhibits minimal protein binding and is minimally metabolized. It is primarily renally eliminated and has a half-life of approximately 17 hours following a single oral dose. Administration of TDF with a high-fat meal results in an increased

bioavailability (increase in AUC and C_{max} of 40% and 14%, respectively). However, administration with a low-fat meal results in similar PK to that seen in a fasted state. Thus, TDF can be administered without regard to food.

The PK properties of tenofovir are comparable between healthy and HIV-1 infected individuals, and between adults and adolescents. Historically variability, as denoted by % CV, is comparable in adults and adolescents. The table below shows the mean pharmacokinetic parameters observed following repeat dosing of TDF 300 mg in HBV infected adolescents in Study 0115 as compared to historical studies in HIV-1 infected adults and adolescents.

Tenofovir Pharmacokinetic Parameters Following Multiple Doses of TDF 300 mg/day in HBV Infected Adolescents, and Comparative Data in HIV-1 Infected Adolescents and Adults

TFV Steady-state PK Parameter	GS-US-174-0115 300 mg/day (N=52)[a]	Historical Data in HIV-1 Infected Adolescents		Historical Adult Data in HIV-1 Infected Adults					
		GS-US-104-0321 300 mg/day (N=8)[b]	GS-01-926 and GS-01-927 300 mg/day (N=7)[b]	GS-97-901 300 mg/day		GS-99-907 300 mg/day			
				8th Dose (N=8)	28th Dose (N=8)	12 Weeks (N=12)	24 Weeks (N=12)	36 Weeks (N=7)	48 Weeks (N=7)
AUC_{tau} (ng•h/mL)[c] Mean (%CV)	3015.2	3390.6 (36.0)	3007.8 (27.8)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	352.7	377.5 (35.6)	268.3 (27.2)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL)[c] Mean (%CV)	—	64.4 (52.6)	63.0 (36.4)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.5	1.98 (1.46, 2.99)	2.08 (1.00, 4.00)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h)[c] Median (Q1, Q3)	19.9	10.54 (9.02, 15.30)	13.99 (7.97, 17.30)	13.7	14.4	14.0	14.9	12.4	14.5

2.3 Analytical

2.3.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tenofovir and the internal standard (tenofovir-d_6) concentrations were determined using fully validated HPLC mass spectroscopy (LC-MS/MS) methods.

2.3.2 Which metabolites have been selected for analysis and why?

Tenofovir was quantified in this study. No metabolites were selected for analysis. TDF is converted to tenofovir *in vivo*. Tenofovir is subsequently phosphorylated intracellularly to its

active moiety, tenofovir diphosphate. Therefore, the measurement of tenofovir in plasma, as a surrogate for its intracellular form, is appropriate.

2.3.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Tenofovir was measured in its total form. Tenofovir exists as approximately 93% unbound in plasma. Thus in this case, the distinction between the measurements of free or total drug is virtually inconsequential since almost all of tenofovir is unbound in plasma.

3 DETAILED LABELING RECOMMENDATIONS

The Applicant's proposed labeling statements for NDA 21356/S-42 are shown in black font. Labeling statements recommended by the Applicant to be removed are shown in ~~black strikethrough font~~. Statements that are recommended to be removed by this Reviewer are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underlined blue font.

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Reviewer's Comment:
The Applicant's proposed revisions to sections 7.1(Drug Interactions) and 12.3 (Assessment of Drug Interactions) of the TDF package insert are acceptable.

4 APPENDIX

4.1 Individual Study Review

4.1.1 GS-US-174-0115

Title
"A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection"

Objectives
The primary objective of this study was a follows:

- To compare the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate 300 mg once daily versus placebo once daily in adolescents (aged 2 to 17 years) with chronic hepatitis B

The secondary objectives of this study were as follows:

- To evaluate the biochemical and serological responses to TDF versus placebo in adolescents with chronic hepatitis B infection
- To evaluate the incidence of drug resistance mutations

Study Design

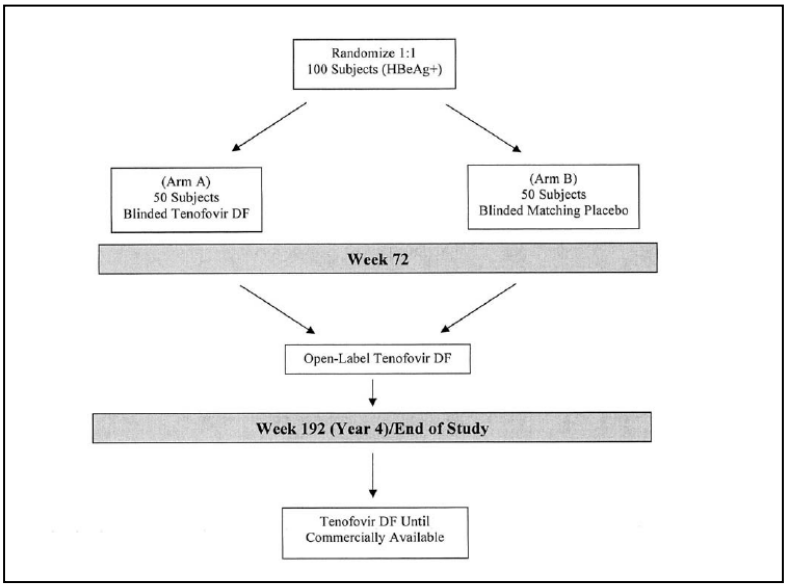
Study 0115 was an international, multicenter study. The first 72 weeks of this study involved a randomized, double-blind, parallel group, treatment period evaluating the safety, efficacy, and tolerability of TDF in adolescent subjects ages 12 to <18 years with HBeAg-positive or HBeAg-negative hepatitis B infection. Subjects were randomized 1:1 to either TDF (Treatment Group A) or placebo (Treatment Group B). Randomization was stratified by age (12 to 14 and 15 to 17 years) and geographical location of study site (North America and Europe).

Reviewer Comment:

The inclusion of a placebo arm in this study is considered acceptable. An estimated 5-10% of pediatric patients with chronic HBV will spontaneously clear hepatitis B early antigen (HBeAg). 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 currently is no clear consensus regarding optimal timing of initiation of treatment in pediatric patients. In addition, since the serious complications of chronic HBV often require years to develop, a placebo-controlled study is not expected to place patients at undue risk and will allow for clearer conclusions regarding efficacy of TDF and a cleaner assessment of safety since TDF will be administered in the absence of other antiretroviral drugs (in contrast to the HIV-infected population).

After completing 72 weeks of treatment in their assigned treatment groups, eligible subjects from both treatment groups were given the option to continue (or initiate) treatment with TDF in a 120-week open-label extension study.

Study GS-US-174 0015 Schema



TDF PK was also assessed in Study 0115. For all subjects one randomly-timed PK sample was collected for analysis of concentration of tenofovir in plasma at each study visit (Wks 4, 8, 16, 24, 32, 40, 48, 56, and 64).

Key Inclusion Criteria

- Male or female
- 12 to <18 years of age
- Documented chronic hepatitis B infection defined as positive serum HBsAg >6 months
- HBV DNA $\geq 10^5$ copies/mL
- HBeAg-positive or HBeAg-negative
- Weight ≥35 kg
- Naïve to tenofovir DF
- ALT ≥2 x ULN at screening, OR any history of ALT ≥2 x ULN over the past ≤24 months
- Estimated GFR (creatinine clearance) ≥ 80 mL/min/1.73m^2 (using Schwartz Formula)
- Adequate hematologic function (absolute neutrophil count ≥1,500/mm^3; hemoglobin ≥10.0 g/dL).

Key Exclusion Criteria

- Pregnant or lactating females
- Sexually-active males and females of reproductive potential who were not willing to use an effective method of contraception during the study
- Decompensated liver disease defined as direct (conjugated) bilirubin >1.2 x ULN, prothrombin time (PT) >1.2 x 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)
- α-fetoprotein >50 ng/mL
- 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
- Evidence of hepatocellular carcinoma
- Co-infection with HIV, HCV, or HDV
- Significant cardiovascular, pulmonary, or neurological disease
- History of solid organ or bone marrow transplantation
- Need for ongoing therapy with any of the following:
    - nephrotoxic agents
    - systemic chemotherapeutic agents
    - systemic corticosteroids (short courses <2 weeks were allowable)
    - interleukin-2 (IL-2) and other immunomodulating agents
    - chronic daily NSAID therapy
    - investigational agents (except with the expressed approval of the sponsor)
- Prior history of significant renal disease (i.e., nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis)
- Prior history of significant bone disease (i.e., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochondroses, multiple bone fractures
- Known hypersensitivity to the study drugs, the metabolite, or formulation excipients

Formulation Used

- Marketed TDF 300 mg strength tablet

Dosage and Administration

- 72 week-randomized, blinded period:
  - Treatment A group received one TDF 300 mg tablet once daily taken orally and without regard to food
  - Treatment B received a matching placebo

- Open-label TDF extension period:
  - All subjects received TDF 300 mg once daily taken orally and without regard to food

In addition, all subjects were instructed to take a daily multivitamin containing 100% RDA of vitamin D throughout the study.

Rationale for Dose Selection

The selection of the 300 mg dose for TDF for use in HBV infected adults was based upon the following rationale: (1) The 300 mg dose has been demonstrated to be the optimal dose of TDF for the treatment of HIV-1 infection; the inhibition constant (Ki) of tenofovir against HIV-1 reverse transcriptase (0.02-1.6 μM) is similar to the Ki against HBV polymerase (0.18 μM); (2) The safety profile of TDF 300 mg once daily has been well characterized in patients with HIV infection, and TDF 300 mg once daily has been shown to be safe in that patient population; (3) Reducing the dose of TDF may lead to an increased risk of the emergence of resistance as documented with other antivirals; (4) In the dose-ranging study GS-98-902, the safety profile of TDF 300 mg once daily was not different from the safety profiles of lower doses of TDF (75 mg and 150 mg); and (5) The safety of the 300 mg dose is similar in HIV-infected patients with or without co-infection with chronic hepatitis B, as supported by study GS-99-910. Further, in the GS-US-174-0102 and GS-US-174-0103 studies, the 300 mg dose of TDF was shown to be an effective dose for treatment of chronic hepatitis B infection in adults with HBeAg-negative/anti-HBe-positive disease and HBeAg-positive disease, respectively.

Studies in HIV-infected children (Studies GS-01-926, GS-01-927 and GS-02-983) indicate that an 8 mg/kg dose in a pediatric population will result in a TDF systemic exposure similar to that in HIV-infected adults receiving the commercially available TDF 300 mg tablet. The recommended oral dose of TDF in children is 8 mg/kg of actual body weight, to a maximum of 300 mg/day (≥ 35 kg). All adolescents in this substudy weighed ≥ 35 kg and received TDF as a 300 mg tablet, administered once daily without regard to food.

Assessments

Pharmacokinetics

One randomly-timed plasma samples was collected from all subjects at each study visit (Baseline and Weeks 4, 8 16, 24, 32, 40, 48, 56, and 64). Samples were obtained at the following time intervals: predose, and 0-0.5, 0.5-1, 1-2, 2-3, 3-4, 4-5, 5-7, 7-9, 9-11, 11-13, 13-15, 15-17, 17-19,

19-21, 21-23, 23-24 hours post-dose. At the time each sample was collected, date and time of last dose taken, whether or not the dose was taken with food, and the date and time of blood draw were recorded. Pooled tenofovir plasma concentrations overall and by age group at study baseline (12 to 14 years, 15 to 17 years) were utilized for the tenofovir pharmacokinetic analysis. Mean and median tenofovir plasma concentration-time profile for each randomization age-group at study baseline were constructed by calculating the mean and median plasma concentrations for the mid-time point of each sample interval. The following pharmacokinetic parameters were estimated using noncompartmental methodology: C_{max}, T_{max}, AUC_{0-24}, and $T_{1/2}$.

Bioanalytical

Concentrations of tenofovir in plasma samples were determined using fully validated high-performance liquid chromatography tandem mass spectroscopy (LC/MS/MS) bioanalytical methods. Assay validation parameters are summarized in the table below.

Bioanalytical Assay Validation Parameters

Parameter	Tenofovir
Linear range (ng/mL)	5 to 3000
LLQ (ng/mL)	5
Interassay precision range (relative SD)	2.4 to 6.5
Interassay accuracy range[a]	–4.7 to 2.0
Stability in frozen matrix (days)	190 days at –20°C and –70°C; 1426 days at –80°C

Efficacy

Primary Endpoint

- HBV DNA <400 copies/mL at Week 72

Secondary Endpoints (Evaluated at Week 48 & 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.

Safety

Primary endpoint

- Cumulative incidence of at least a 6% decrease from baseline in bone mineral density of the spine through Week 72

Secondary endpoints

- Cumulative incidence of at least a 6% decrease from baseline in bone mineral density of the whole body through Week 72
- Cumulative incidence of at least a 6% decrease from baseline in bone mineral density of the spine through Week 48
- Cumulative incidence of at least a 6% decrease from baseline in bone mineral density of the whole body through Week 48
- Corresponding changes in Z-scores

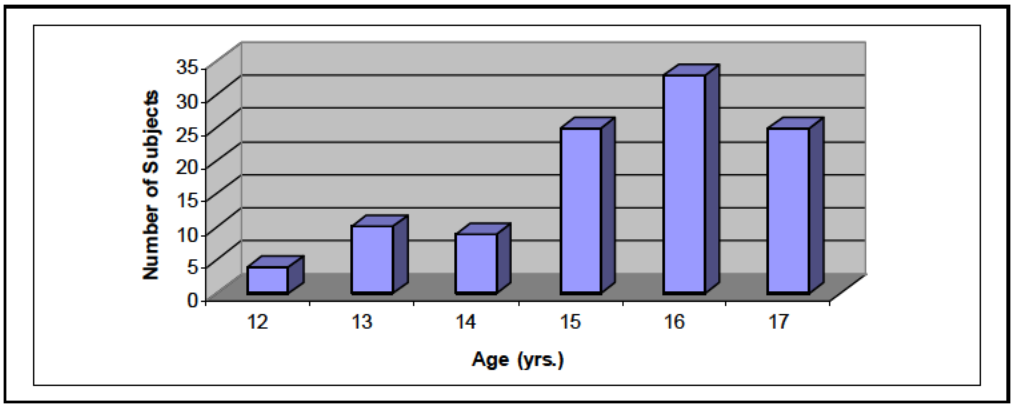
Other safety endpoints included: change from baseline in lumbar spine BMD, percent change from baseline in bone mineral density of whole body; development of drug-resistant mutations. In addition, adverse events and clinical laboratory tests were collected at every study visit.

Results

This was an international and multicenter study with a total of 21 clinical sites which included sites in the following countries: Poland (8), Romania (3), United States (3), Bulgaria (2), France (2), Spain (2), and Turkey (1).

A total of 106 subjects (52 in the TDF group and 54 in the placebo) were randomized in the study and 101 subjects (51 in the TDF group and 50 in the placebo group) completed the double-blind treatment period through Week 72. The majority of subjects were Caucasian (92.5%), male (68.9%) and were enrolled in clinical sites in Europe (95.3%). Subjects were predominantly between the ages of 15 and 17 years (78.3%), with an overall mean age of 15 years). The following figure displays the baseline age distribution of subjects enrolled in Study 0115.

Study 0115 Age Distribution



Bioanalytical

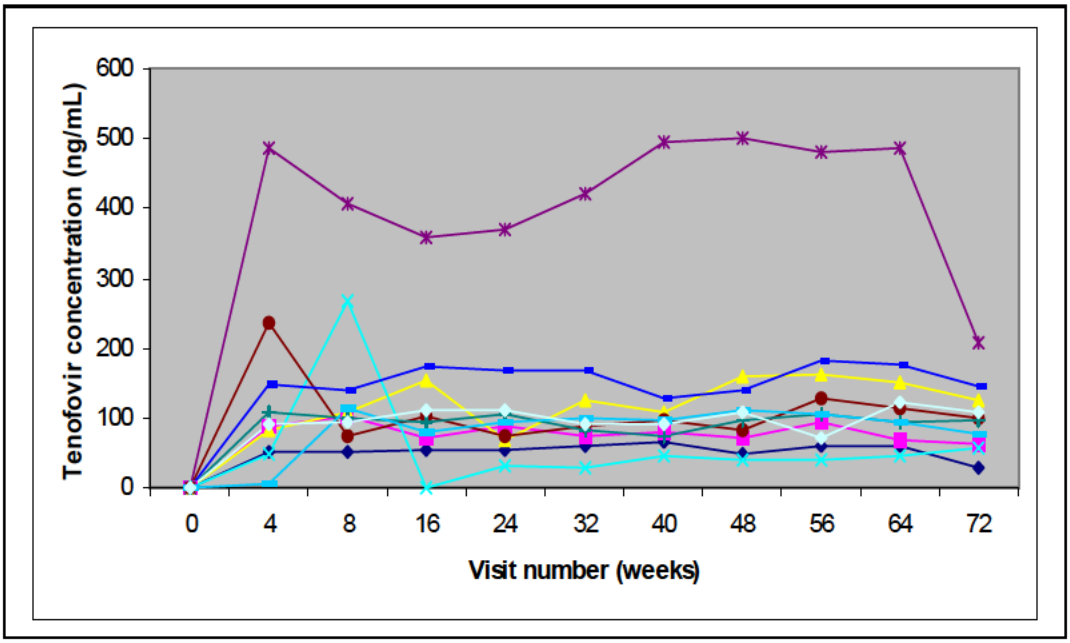
The human plasma samples were analyzed for tenofovir using LC/MC/MS methodologies validated by (b) (4). All sample analysis runs met the pre-specified data acceptance criteria.

The long-term stability of tenofovir was demonstrated in human plasma stored at -80˚C for 1426 days. The study samples were stored for a maximum of 826 days. All samples were analyzed in the timeframe supported by frozen stability data.

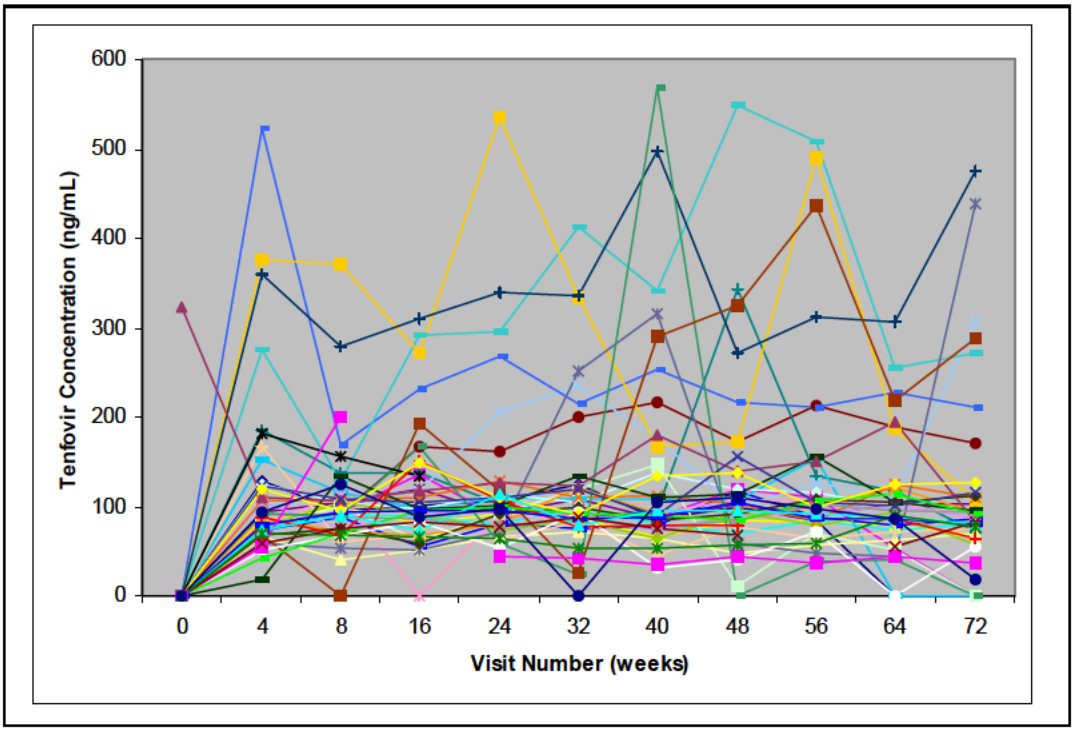
Pharmacokinetics

Fifty-two subjects received TDF during the 72 Week, randomized treatment period and all contributed PK samples (1 randomly timed sample at each study visit) for analysis of tenofovir concentrations. The following figures display the tenofovir plasma concentrations at each study visit for the 12 to 14 years old and 15 to 17 year old age groups, respectively.

Tenofovir Concentrations (Randomly-Timed Plasma Samples) in the 12 to 14 Year Old Age Group (N=10)



Tenofovir Concentrations (Randomly-Timed Plasma Samples) in the 15 to 17 Year Old Age Group (N=42)



The following table shows the mean and median tenofovir PK parameters obtained from pooled data overall and by age groups.

Mean and Median Tenofovir Pharmacokinetic Parameters Overall and by Age Group

Age Category	AUC_{tau} (ng-hr/ml)	C_{max} (ng/ml)	$T_{1/2}$ (hr)	T_{max} (hr)
Overall				
Mean	3015.2	352.7	19.2	1.5
Median	2884.1	341.0	19.9	1.5
15–17 years				
Mean	2904.6	306.6	15.4	1.5
Median	2813.2	370.0	19.5	0.25
12–14 years				
Mean	-	444.7	-	1.5
Median	-	480.0	-	1.5

Due to a lack of data over a wide range of sampling interval (see table below), AUC and half-life determinations were not performed in adolescents 12 to 14 years of age subset.

Number of Pharmacokinetic Samples Collected For Each Time Interval By Age Group

Sampling Time Interval (hours)	Number of Samples		Number of Subjects Contributing Samples	
	12 – 14 yr. age group	15 – 17 yr. age group	12 – 14 yr. age group	15 – 17 yr. age group
Pre-dose	10	44	10	34
0 to 0.5	1	6	1	4
0.5 to 1	2	10	2	3
1 to 2	9	18	1	6
2 to 3		22		9
3 to 4		14		6
4 to 5		11		4
5 to 7		3		3
7 to 9		4		1
9 to 11	2	15	1	7
11 to 13	26	106	6	22
13 to 15	36	75	5	22
15 to 17	6	52	3	12
17 to 19		14		6
19 to 21		1		1
21 to 23	1	4	1	3
23 to 24	5	10	1	4

Pooled tenofovir exposures in the adolescent subjects in this study were comparable to exposures achieved from historical studies in HIV-1 infected adults and adolescents (see table below).

Tenofovir Pharmacokinetic Parameters Following Multiple Doses of TDF 300 mg/day in HBV Infected Adolescents, and Comparative Data in HIV-1 Infected Adolescents and Adults

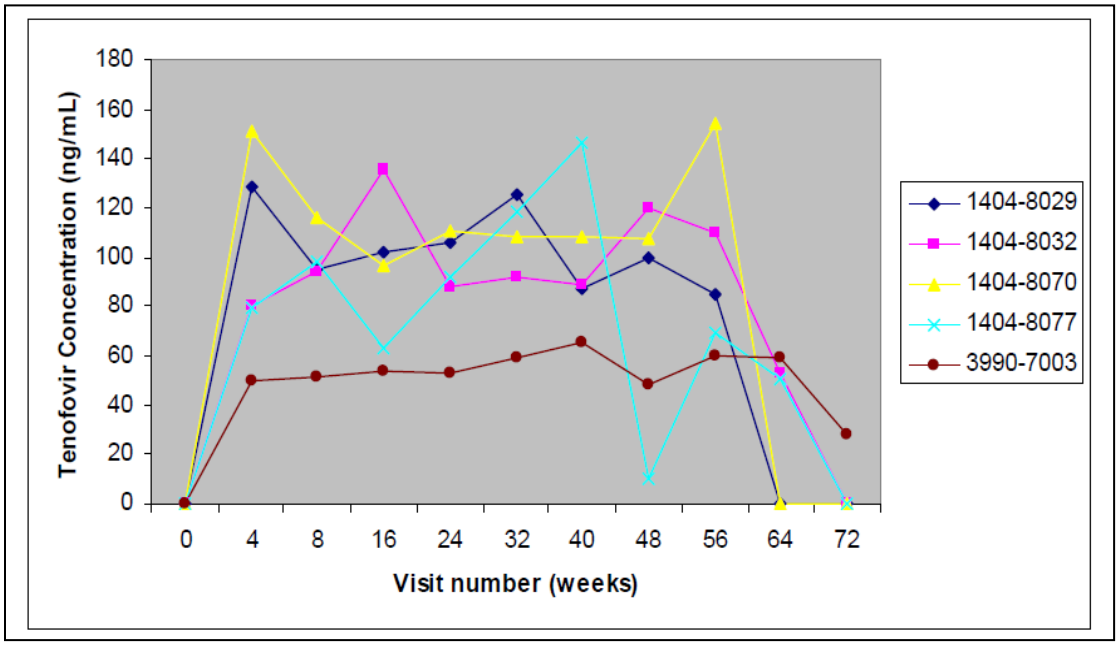
TFV Steady-state PK Parameter	GS-US-174-0115 300 mg/day (N=52)[a]	Historical Data in HIV-1 Infected Adolescents		Historical Adult Data in HIV-1 Infected Adults					
		GS-US-104-0321 300 mg/day (N=8)[b]	GS-01-926 and GS-01-927 300 mg/day (N=7)[b]	GS-97-901 300 mg/day		GS-99-907 300 mg/day			
				8th Dose (N=8)	28th Dose (N=8)	12 Weeks (N=12)	24 Weeks (N=12)	36 Weeks (N=7)	48 Weeks (N=7)
AUC_{tau} (ng•h/mL)[c] Mean (%CV)	3015.2	3390.6 (36.0)	3007.8 (27.8)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	352.7	377.5 (35.6)	268.3 (27.2)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL)[c] Mean (%CV)	—	64.4 (52.6)	63.0 (36.4)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.5	1.98 (1.46, 2.99)	2.08 (1.00, 4.00)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h)[c] Median (Q1, Q3)	19.9	10.54 (9.02, 15.30)	13.99 (7.97, 17.30)	13.7	14.4	14.0	14.9	12.4	14.5

Efficacy

One-hundred six subjects (N=52 TDF, N=54 placebo) were randomized in Study 0115 and were included in the ITT population. At Week 72, 88.5% of TDF treated subjects achieved the primary endpoint of HBV DNA <400 copies/mL as compared to 0% of placebo treated subjects. Eighty-five percent of TDF treated subjects as compared to 0% of subjects in the placebo group achieved the secondary endpoint of HBV DNA <169 copies/mL at Week 72 (see Clinical Review authored by Dr. Prabha Viswanathan for further information regarding efficacy results).

Five subjects were classified as virologic failures (HBV DNA >400 copies/mL at Week 72). Of the five, one subject was never suppressed (Subj. 3990-7003), one had unconfirmed virologic breakthrough (Subj. 1404-8077) and three had confirmed virologic breakthrough (Subj. 1404-8032, 1404-8029, and 1404-8070). All instances of virologic breakthrough were felt to be attributed to nonadherence, as indicated by low tenofovir plasma levels (see Graph below).

Tenofovir Concentrations in TDF Treated Subjects Classified as Virologic Failures at Week 72 (N=5)



Safety

The adverse events observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials of TDF in adults. There were no deaths reported. Decreases in median BMD Z-scores were observed in TDF-treated adolescents in this trial. However, no patients in either treatment group met the primary safety endpoint of ≥6% decrease from baseline bone mineral density of the spine through Week 72 (see Clinical Review authored by Dr. Prabha Viswanathan for further information regarding safety results).

Conclusions

Tenofovir exposures following once daily oral administration of the TDF 300 mg tablet in HBV infected adolescent subjects ages 12 to <18 years were comparable to that observed in HIV-1

infected adults and adolescents receiving the same dose. The primary efficacy endpoint of (HBV DNA <400 copies) was met for the majority of TDF treated subjects (88.5%) by Week 72 and for none of the placebo treated subjects. TDF was relatively well-tolerated in this population and no new safety concerns were identified. Together, these findings confirm the appropriateness of a TDF 300 mg once daily dosing regimen for the treatment of chronic hepatitis B infection in adolescent patients.

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/s/

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07/19/2012

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07/19/2012