Clinical Review and Cross-Discipline Team Leader Summary Review

Date	November 21, 2018
From	Samer El-Kamary, MD, MPH Wendy Carter, DO
Subject	Clinical and Cross-Discipline Team Leader Review
NDA # and Supplement#	NDA 021356 – Supplement 57
Applicant	Gilead Sciences, Inc.
Date of Submission	6/14/2018
PDUFA Goal Date	December 14, 2018
Proprietary Name	Viread(R)
Established or Proper Name	Tenofovir disoproxil fumarate (TDF)
Dosage Form(s)	TDF 150, 200, 250, and 300 mg tablets TDF 40 mg/gram oral powder
Applicant Proposed Indication(s)/Population(s)	Treatment of Chronic Hepatitis B Infection in children 2 to <12 year old
Applicant Proposed Dosing Regimen(s)	8 mg/kg PO once daily
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Chronic Hepatitis B Infection in children 2 to <12 year old
Recommended Dosing Regimen(s) (if applicable)	8 mg/kg PO once daily

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
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 children 2 to < 12 years of age weighing ≥ 10 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. The efficacy results suggest a clear benefit of TDF over placebo. Consistent with prior TDF trials, the results of DEXA scans and biochemical assessments of bone turnover suggest negative effects on bone mineral density. However, the clinical significance the TDF effect on bone metabolism is unclear. Additionally, the long-term effects on growth and fracture risk are unknown, particularly for the youngest patients who may have long-term TDF exposure during their active bone development years. However, there are limited long term data (6.5 years) in pediatric HIV-1 infected patients showing that these effects stabilize within 2 years and that there are overall increases in bone mineral density. These data support the bone safety in chronic HBV and are similar to findings in adolescents and adults. Renal toxicity, which is well-described among HIV-1 infected patients, was not observed in this CHB study, albeit, this is a relatively small study. No patients demonstrated a 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 and we recommend approval of tenofovir disoproxil fumarate (TDF, Viread®) for the treatment of Chronic Hepatitis B infection in children 2 to < 12 years of age weighing ≥ 10 kilograms.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic HBV (CHB) infection remains a significant global health cause of chronic liver disease, cirrhosis, hepatocellular carcinoma and death. • Hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure, and the majority of pediatric HBV infections in the US are the result of vertical transmission • Up to 95% of perinatally infected children are expected to develop CHB infection.	Chronic HBV infection remains a major cause of morbidity and mortality worldwide. It is particularly serious when acquired in childhood, given the likelihood of developing serious or fatal complications by early adulthood. This can result in a debilitating disease at the prime productive years of an individual, with significant limitations in a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Children with active CHB inflammation are at a high risk of liver fibrosis and cirrhosis, and given their early infection, the likelihood of developing these complications by early adulthood is very high. • While universal hepatitis B virus (HBV) vaccination is safe, affordable and highly effective, it is only useful if given prior to infection. • Although the proportion of children 2 to <12 years or older who will be recommended for treatment are relatively few, additional treatment options are still needed.	person's professional and personal activities, disability, reduced healthy life expectancy, and potential years of life lost.
Current Treatment Options	• There are several approved drugs for HBV infection. Each of these treatments have advantages and limitations. • Interferon alfa-2b and pegylated interferon alfa-2a are approved for children ≥ 1 year and ≥ 3 years of age, respectively. Their advantage is that they have a finite duration of therapy, but have poor tolerability and safety profile, and are curative in only a small fraction. • Lamivudine is approved for children ≥ 2 years of age but is not a preferred drug due to high rates of viral resistance. • Entecavir is approved for children > 2 years of age and has a low rate of drug resistance, but has a higher rate of resistance if used after lamivudine. Furthermore, its efficacy is around only 40-49% in all age groups. • Adefovir is not preferred because of its weak antiviral activity and renal toxicity that limits dosing. Furthermore, it is only approved for ≥ 12 years of age. • Telbivudine is only approved for ≥ 16 years of age, thereby not available to younger age groups. • Tenofovir disoproxil fumarate (TDF) is approved for children ≥ 12 years of age and has a high efficacy, but causes a slower gain in bone mineral density over time.	There are multiple treatment options for children infected with CHB. However, only one other drug (entecavir) is available as an oral medication with moderate efficacy for children 2 to < 12 years old. The availability of another oral therapy, especially one with a higher efficacy is highly desirable.
Benefit	• To support an efficacy claim for the use of TDF (Viread) for the treatment of children with chronic hepatitis B (CHB) infection in children 2 to < 12 years old, the applicant submitted the 48 Week efficacy and safety results from a single study (Study Trial GS-US-174-	TDF was highly efficacious in suppressing HBV in children 2 to < 12 years old. This viral suppression led to a higher proportion of subjects with ALT normalization, which is reflective of reduced

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	0144), which is a Phase 3, randomized, double-blind, placebo-controlled trial. • In this study, 89 HbeAg positive (96%) and negative (4%) subjects aged 2 years to less than 12 years of age with chronic HBV infection were treated with VIREAD 8 mg/kg up to a maximum dose of 300 mg (N=60) or placebo (N=29) once daily for 48 weeks. • The study demonstrated that a significantly greater proportion of subjects in the TDF group achieved the primary endpoint of HBV DNA < 69 IU/mL at Week 48 compared with the placebo group (77% vs. 7%). TDF treatment also led to a higher proportion of subjects with ALT normalization at Week 48 than placebo (66% vs. 15% by central lab standard).	hepatic inflammation. Given the long-term studies in adults, a long-term suppression of HBV virus reduces subsequent liver inflammation and fewer long-term complications such as fibrosis, cirrhosis, liver failure and hepatocellular complications. It is reasonable to assume that long-term viral suppression in children 2 to < 12 years old would also lead to fewer complications later in their life.
Risk and Risk Management	TDF has a few known noteworthy side-effects: • A slower gain in bone mineral density compared to children receiving placebo which seem to stabilize after two years of therapy. While this could have an impact on skeletal height and possible increased risk of fractures, there was no evidence of these complications in this study. However, long-term effects, particularly in younger children, are still unknown. • Some initial elevations in liver enzymes are expected that later regress after continued treatment. • Renal toxicity is a well-described complication of TDF therapy, but was not seen in this study, where there was no significant difference compared to placebo recipients.	The frequency of side-effects observed in this study were similar to those noted in adolescents and adults, and did not demonstrate an increased risk compared to those in older age groups. The bone mineral density reduction seems to stabilize over time, and other side-effects (e.g., liver enzyme elevation) improve with continued treatment. Based on the available safety profile for TDF, no Risk Evaluation and Mitigation Strategy (REMS) is recommended at this time.

2. Background

This review summarizes the 48 week efficacy and safety data from Study Trial GS-US-174-0144: A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection.

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 younger pediatric patients. (Terrault NA, 2018) Although the proportion of children 2 to ≤12 years or older who will be recommended for treatment are relatively few, additional treatment options are still needed.

Viread® (tenofovir disoproxil fumarate; TDF) is an oral prodrug of tenofovir (TFV), a nucleotide reverse transcriptase. After absorption, TDF is rapidly converted to TFV, which is metabolized intracellularly to the active metabolite, TFV diphosphate, a potent and selective inhibitor of both hepatitis B virus (HBV) polymerase and human immunodeficiency virus type-1 (HIV-1) reverse transcriptase.

TDF is approved for treatment of chronic hepatitis B (CHB) in adults and pediatric patients ≥ 12 years old in the United States (US) and the European Union (EU). (VIREAD®, 2017) TDF in combination with other antiretroviral agents is also approved for the treatment of HIV infection in adults and pediatric patients ≥ 2 years in the US and the EU. The current indication for TDF excludes patients younger than 12 years old with CHB.

This supplemental NDA (sNDA) is submitted to Viread NDA 021356/022577 to expand the indication to the pediatric population 2 to ≤ 12 years old with CHB based on new 48 week interim safety and efficacy data from the ongoing Phase 3 Study Trial GS-US-174-0144 (Trial 0144) included in this application. The sponsor submits these data to support the use of TDF in this population without the addition of any clinically meaningful risk.

2.1. Product Information

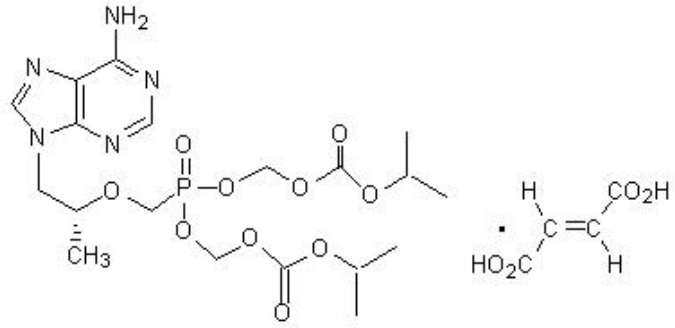
VIREAD® is the brand name for tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog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

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.

2.2. Tables of Currently Available Pediatric Treatments for Proposed Indications

To date, the only approved oral products for the treatment of CHB in pediatric patients are summarized in Table 1. Each of these treatments has significant limitations including rapid development of resistance (lamivudine), weak antiviral activity and renal toxicity that limits dosing (adefovir), poor tolerability and safety profile (interferon alfa-2b; and pegylated interferon alfa-2a), or are not available to those < 16 years old (telbivudine). Therefore, better treatment options are needed for this population.

Table 1. Drugs Approved for Chronic Hepatitis B Infection

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
Pegylated interferon alfa-2a	Pegasys®	180 micrograms/1.73 m^2 SQ once weekly	≥ 3 years 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	≥ 2 years of age

Telbivudine	Tyzeka®	600 mg once daily	≥ 16 years of age
Tenofovir disoproxil fumarate	Viread®	300 mg once daily	≥ 12 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 children > 12 years of age and 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 of age before determining whether it is appropriate to study TDF for HBV in the birth to <2 years age group. On August 10, 2015, the PREA PMR for subjects with CHB ages birth to < 2 years of age was released because the study was determined to be impossible or highly impractical for pediatric patients in this age group. This was because the number of HBV infected pediatric patients less than 2 years of age is small, and the drug is not likely to be used in a substantial number of pediatric patients in this age group. Therefore, FDA waived the pediatric study requirement for ages birth to <2 years of age.

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 to fulfill a portion of that Written Request and PREA Postmarketing Requirement (PMR) 283-1: Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 12 to < 18 years of age (Study GS-US-174-0115). The application was approved on August 16, 2012.

This current submission pertains to Trial 0144 evaluating Viread in pediatric patients (ages 2 to < 12 years) and was conducted in accordance with postmarketing requirement (PMR) 283-2 under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) as a required pediatric study to provide data for the treatment of CHB in pediatric patients 2 to < 12 years of age. This study, along with the Viread HBV adolescent study GS-US-174-0115, also addressed PMR 1618-1 under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) relating to the further investigation of whether changes in bone mineral density (BMD) observed with TDF are

secondary to renal phosphate excretion, or effects on bone. Furthermore, in accordance with the FDA's request dated 27 March 2018 (Reference ID: 4239299) for a prior approval supplement to update the Viread label in accordance with the Pregnancy and Lactation Labeling Rule (PLLR) format, Gilead included in this submission the draft labeling text to comply with the PLLR format.

Summary of Study Protocol

The original study protocol (22 July 2011) was a prospective, randomized, double-blind, placebo-controlled trial to compare the antiviral efficacy, safety, and tolerability of TDF to placebo in pediatric patients with chronic HBV infection. One hundred (100) TDF-naïve pediatric patients aged 2 to < 12 years, at the time of enrollment, with chronic HBV infection (either HBeAg-positive or HBeAg-negative), HBV DNA $\geq 10^5$ copies/mL AND either ALT $\geq 2 \times$ ULN at screening OR any history of ALT $\geq 2 \times$ ULN over the past ≤ 24 months were eligible for enrollment. These patients were to be randomized in a 1:1 ratio to treatment arm A or B:

- Treatment A (n = 50): TDF PO once daily for 72 weeks
- Treatment B (n = 50): matching placebo PO once daily for 72 weeks

After 72 weeks of blinded randomized treatment, each subject was to be switched to open-label TDF treatment for an additional 120 weeks (2.5 years). The duration for a given subject is to be at least 4 years (each subject will receive a total of 192 weeks of study drug treatment).

Randomization was to be stratified by age (2 to < 6 and 6 to < 12, at the time of enrollment), geographical location of study site (North America/Europe and Asia) and, treatment naïve and treatment experienced.

The primary analysis was to be conducted at the completion of double-blinded treatment, after the last randomized subject reached Week 72. Subsequently, ongoing efficacy and safety analyses of all subjects continuing on open-label TDF was to be performed after the last randomized subject reached Weeks 144 and 192, respectively.

An external independent multidisciplinary Data Monitoring Committee (DMC) reviewed the progress and safety of this study approximately every 24 weeks following the time of randomization of the first subject and will continue to do so until the end of the study. At each meeting, the DMC reviewed (and will continue to review) routine safety and DEXA data and will make recommendations regarding modification of study treatment.

Protocol Amendments

The original study protocol was amended 4 times. Key changes to the protocol for each amendment were as follows:

- The protocol was amended for the first time on 07 March 2012; key changes at Amendment 1 were primarily updates to/clarification of study objectives, eligibility criteria, study procedures, and use of concomitant medications and oral contraception.
- The protocol was amended for the second time on 08 November 2012. Key changes in Amendment 2 included updates to the design and conduct of the PK substudy in response to regulatory authority comments.
- The protocol was amended for the third time on 29 February 2016. At this time, due to difficulty enrolling subjects, to limit exposure of subjects to placebo, and upon agreement of the FDA that

approximately 90 subjects (randomized 2:1 to TDF:Placebo) would be sufficient to conduct the study, the primary efficacy endpoint was changed from Week 72 to Week 48. The amendment specified that upon completing 48 weeks of blinded treatment, all subjects would switch to open-label TDF for the remainder of the study, and subjects who were beyond Week 48 under the previous protocol would switch to open-label TDF at Week 72 (as originally planned). All subjects would receive open-label TDF until Week 192 (end of study).

- The protocol was amended for the fourth time on 04 August 2016. At that time, an extension phase was added, whereby all subjects who completed the study were offered the opportunity to continue receiving open-label TDF until the time that TDF became commercially available for patients of their age and weight in the country of their enrollment, and that subjects were to attend study visits every 12 weeks.

2.6. Other Relevant Background Information

TDF was originally developed as a nucleotide reverse transcriptase inhibitor for treatment of HIV-1 infection. On October 26, 2001, TDF was approved for treatment of HIV-1 infection in adults in combination with other antiretroviral drugs (ARVs). A Written Request 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 HIV-infected children 2 years and older on January 18, 2012 (sNDA 021356/S-038, NDA 022577/S-001).

3. Product Quality

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

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology

A brief description of the Clinical Pharmacology review is included here. Please refer to Dr. Su-Young Choi's Clinical Pharmacology Review for full details.

In this study, population PK modeling was conducted to describe the plasma PK for tenofovir in pediatric CHB patients and to explore exposure-response relationships. Sparse PK samples were collected from 58 subjects at study visits from Weeks 4 through 48 for tenofovir. Based on the population pharmacokinetic analysis, tenofovir AUC_{tau} and C_{max} values were comparable between pediatric CHB patients and pediatric HIV patients after accounting for drug interactions between lopinavir/ritonavir and TDF in pediatric HIV patients.

Exposure-response analyses were conducted for efficacy and safety. In addition, several analyses were conducted by the review team to see whether lower efficacy in younger pediatric patients (2 to < 6 years old) was potentially due to lower TFV exposures. The analyses using multiple regression models as well as

exposure-response analysis within the same age groups indicated that exposure itself is unlikely to be associated with the lower efficacy in the younger age group. As for safety (changes in BMD in spine or whole body), there was no exposure-response relationship observed among patients who received TDF.

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

A brief summary of the statistical review and assessment of efficacy is provided here. Please refer to Dr. Karen Qi's statistical review for full details.

This application included an interim Week 48 clinical study report for Trial 0144, a Phase 3, randomized and double-blinded study. Pediatric patients were randomized in a 2:1 ratio to receive either TDF or placebo daily for 48 weeks. All patients switched to receive open-label TDF after Week 48. The primary efficacy endpoint was the proportion of subjects with HBV DNA < 69 IU/mL at Week 48.

Trial 0144 enrolled an ethnically diverse population from Europe (Romania and Bulgaria), Asia (South Korea and India) and the United States. The 60 subjects randomized to the TDF group had 22 (36.7%) children < 6 years old, 45.0% were female, 68.3% were Asian [15% were Indian and 53.3% were non-Indians], 6.7% were Black or African American, and 25.0% were White. Of the 29 subjects randomized to the Placebo group, 11 (37.9%) subjects were < 6 years old, 41.4% were female, 58.6% were Asian [17.2% were Indian and 41.4% were non-Indian], 3.4% were Black or African-American, and 37.9% were White. All subjects were non-Hispanic.

In this study, 89 HbeAg positive (96%) and negative (4%) subjects aged 2 years to less than 12 years of age with chronic HBV infection were treated with VIREAD 8 mg/kg up to a maximum dose of 300 mg (N=60) or placebo (N=29) once daily for 48 weeks. At trial entry, the mean HBV DNA was 8.1 $\log_{10}$ IU/mL and mean ALT was 123 U/L.

The study demonstrated that a significantly greater proportion of subjects in the TDF group achieved HBV DNA < 69 IU/mL at Week 48 compared with the placebo group (77% vs. 7%). TDF treatment also led to a higher proportion of subjects with ALT normalization at Week 48 than placebo (66% vs. 15% by central lab standard). However, the two treatment groups had a similar proportion of subjects with HBeAg loss (30% vs. 28%) or proportion of subjects with HBeAg seroconversion (25% vs. 24%) at Week 48 (Table 2). However, during the clinical review, it was noticed that efficacy in children 2 years to less than 6 years of age was less than that in children 6 years to less than 12 years of age (Table 2).

Table 2. Outcomes of Randomized Treatment (Trial 0144) in the overall cohort, and in children 2 years to < 6 years and 6 years to < 12 years of age.

Endpoint at Week 48	Viread N=60	Placebo N=29
HBV DNA <400 copies/mL (69 IU/ml)		
2 to < 12 years (total)	46/60 (77%)	2/29 (7%)
2 to < 6 years	12/22 (55%)	1/11 (9%)
6 to < 12 years	34/38 (89%)	1/18 (6%)
ALT Normalization[1]		
2 to < 12 years (total)	37/58 (64%)	4/27 (15%)
2 to < 6 years	10/22 (45%)	2/11 (18%)
6 to < 12 years	27/36 (75%)	2/16 (13%)
HBeAg loss[2]	17/56 (30%)	8/29 (28%)
HBeAg seroconversion[2]	14/56 (25%)	7/29 (24%)

Source: Table from Dr. Karen Qi Biostatistical Reviewer
[1] Normal ALT was defined as ≤ 34 U/L for females 2-15 years or males 1-9 years old, and ≤ 43 U/L for males 10-15 years. The ALT Normalization analysis excluded 2 treated subjects who had normal ALT at baseline.
[2] The analysis excluded 4 subjects who were HBeAg negative and HBeAb positive at baseline

The clinical team requested the applicant to provide the potential reasons for the lower response rate for TDF treatment in the younger children than that in the older children. The applicant's response (02 November 2018) was as follows:

1) In the < 6 years old subgroup, 10 out of 22 subjects (45%) receiving TDF treatment were considered treatment failures at Week 48, including five subjects (23%) who had missing data at Week 48 and five subjects (23%) who did not achieve HBV DNA < 69 IU/mL at Week 48.

    a. Of the five subjects who had missing data at Week 48, four subjects withdrew from the study before Week 48 and one subject remained in the study. The subject remaining in the study missed Week 48 visit, achieved HBV DNA < 69 IU/mL at Week 40, and remained HBV DNA < 69 IU/mL at all subsequent time points when assessed through Week 144.

    b. Of the five subjects who did not achieve HBV DNA < 69 IU/mL at Week 48, three subjects had a delayed treatment response and achieved HBV DNA < 69 IU/mL after Week 48.

2) In the ≥ 6 years old subgroup, no subjects had missing data at Week 48.

In summary, the updated data showed that four out of the 10 subjects receiving TDF treatment in the < 6 years old subgroup who were considered treatment failures at Week 48 actually achieved HBV DNA < 69 IU/mL after Week 48. While this information is reassuring in that the lower efficacy can possibly be attributed to a delayed treatment response rather than a true failure, however, in the reviewer's opinion, the updated data for these subjects cannot be used in the Week 48 analysis since the updated data are unavailable for the remaining subjects in the study.

In conclusion, and based on the Week-48 virology data from Trial 0144, submitted in this efficacy supplemental NDA package, the reviewer concluded that there were no statistical issues and that TDF monotherapy appeared

to have antiviral efficacy (achieving HBV DNA <69 IU/mL) in pediatric subjects aged 2 to <12 years, comparable to those observed at Week 48 in TDF-treated adult subjects (Studies GS-US-174-0102 [NCT00117676] and GSUS- 174-0103 [NCT00116805]) and adolescent subjects (12 to <18 years old and weighing ≥35 kg; GS-US-174-0115 [NCT00734162]).

8. Safety

8.1. Overview and Methods

8.11 Safety Summary

Trial 0144 demonstrated that TDF is a well-tolerated treatment for CHB in children 2 to < 12 years old. 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 HBV and HIV patients.

A decline in bone mineral density (BMD) in adults and slower gain in adolescents is a well-known AE associated with TDF exposure. Similar to adolescents, patients in both treatment groups gained BMD, but Placebo 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 is clearly demonstrated by the mean percent change (standard deviation, SD) from baseline in the:

Spine BMD

Week 24: TDF: +1.4 (5.20), Placebo: +4.0 (4.27), *p-value*= 0.025

Week 48: TDF: +3.8 (5.91), Placebo +7.6 (4.98), *p-value* = 0.007

Whole Body BMD

Week 24: TDF +1.4 (4.07), Placebo +4.4 (3.69), *p-value* = 0.002

Week 48: TDF +4.5 (4.86), Placebo +8.9 (5.12), *p-value* <0.001

There was no evidence of clinical implications of this slower BMD gain during the conduct of the trial, but it is unclear whether it will have long-term implications. Because of the unknown long-term effects of this slower BMD gain on skeletal growth (height) and risk of fracture, the product labeling was clarified to include that these risks remain unknown, particularly for the younger age cohort who may have long term exposure during active bone growth. Additionally, labeling states that in the pediatric trials, normal skeletal growth (height) was not affected, however, this was clarified by adding that this finding was limited to the duration of the clinical trials.

Graded hepatic abnormalities presented as elevations in ALT, AST and alkaline phosphatase. There was an ALT flare in 4 TDF subjects and one Placebo subject. All of these subjects had an elevated ALT at baseline and their total bilirubin levels remained normal. Most hepatic laboratory AEs were Grade 1 or 2 in severity.

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.

8.12 Studies/Clinical Trials Used to Evaluate Safety

The results of Trial 0144, a single Phase 3, randomized, double-blind placebo controlled clinical trial of TDF-naïve Hepatitis B infected children 2 to < 12 years old, were reviewed to evaluate the safety of TDF. The Safety Analysis Set, which was used to perform the analyses in this review, included 89 of 90 randomized

subjects who received at least one dose of study drug (one subject randomized to the placebo group was below 2 years of age at the time of the baseline visit and was not treated).

The source of data for the safety review is from Trial 0144. Using the Applicant's STDM and ADAM datasets, the primary clinical reviewer conducted all safety analyses presented in this section using MAED, JReview 13.1.0 and/or JMP Clinical 6.0, unless otherwise specified.

Safety data are presented for 89 subjects treated with TDF (n = 60) or Placebo (n = 29) in Trial 0144 as of the data cut for the Week 48 interim analysis (10 August 2017), except BMD and clinical laboratory data, which were collected up to the data finalization date (16 January 2018). All 60 subjects in the TDF group and 29 subjects in the Placebo group received at least 1 dose of study treatment and were included in the Safety Analysis Set.

8.13 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary version 20.1 used by the Applicant. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms.

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

Not applicable.

8.2. Deaths

No deaths occurred up to 48 weeks of treatment.

8.3. Serious Adverse Events

A total of 17% of subjects in the TDF group and 7% in the Placebo group had an SAE (Table 3). The only SAE reported for > 1 subject in either treatment group was ALT increased (4 subjects in the TDF group and 1 subject in the Placebo group). For 3 subjects in the TDF group and 1 subject in the Placebo group, the AEs of increased ALT were assessed as related to the study drug by the investigator. The majority of reported AEs were considered mild or moderate in severity and did not lead to treatment discontinuation.

Table 3. Overall Summary of Adverse Events During the Double-Blind Treatment Phase (Safety Analysis Set)

	TDF (N=60)	Placebo (N=29)
Any AE*	47 (78%)	17 (59%)
Maximum Toxicity Grade		
Grade 1 (mild)	32 (53%)	12 (41%)
Grade 2 (moderate)	11 (18%)	3 (10%)
Grade 3 (severe)	4 (7%)	2 (7%)
Grade 4 (life-threatening)	0	0
Deaths	0	0
Any SAE	10 (17%)	2 (7%)
Drug-related SAE	3 (5%)	2 (7%)
Drug-related AEs	9 (15%)	4 (14%)
Drug-related Grade 2 AE	2 (3%)	0
Drug-related Grade 3 AE	1 (2%)	2 (7%)
AE Leading to Premature Discontinuation	0	2 (7%)
AE Leading to Temporary Interruption	1 (2%)	1 (3%)

Source: Independent analysis of the ADAE (Adverse Events Analysis) dataset
* Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1 (01 April 2015)

Only 3 SAEs (elevated ALT) and 1 SAE of Grade 3 hypoglycemia were reported for a subject in the Placebo group, and were assessed by the investigator as related to the study drug and led to premature discontinuation of the study drug. Otherwise, all of the other SAEs were assessed as unrelated to study drug, did not lead to discontinuation or modification of study drug, and had resolved at the time of data finalization.

8.4. Dropouts and/or Discontinuations Due to Adverse Events (AEs)

No subjects prematurely discontinued TDF due to AEs. Two subjects in the Placebo Group prematurely discontinued the Placebo due to two AEs: 1 subject with hypoglycemia, and 1 subject with elevated ALT. Two other subjects had a temporary interruption of the study drug (2 or 3 days) due to nonserious AEs, including 1 subject with pyrexia (TDF group) and 1 subject with vomiting (Placebo group). Both AEs were Grade 1 and unrelated to the study drug, and both resolved within 2 days of onset.

8.5. Treatment Emergent Adverse Events and Adverse Drug Reactions

A total of 47 (78%) subjects in the TDF group and 17 (59%) in the Placebo group were assessed as Treatment-Emergent AEs (TEAEs). Of those, 9 (15.0%) subjects in the TDF group and 4 subjects (14%) in the Placebo group were assessed as related to the study drug by the investigator (Table 3). There were 3 (5%) subjects in the TDF group and 2 (7%) in the Placebo group with Grade 2 or 3 TEAEs that were related to the study drug. There were no Grade 4 TEAEs related to the study drug.

The only study-related TEAE that was reported for > 1 subject in either treatment group was increased ALT: 4 subjects (7%) in the TDF group and 2 subjects (7%) in the Placebo group.

8.6. Laboratory Findings Safety Analyses

Almost all subjects had at least one laboratory abnormality: 96.7% in the TDF group and 100.0% in the Placebo group. The majority of laboratory abnormalities were Grade 1 (mild) or 2 (moderate) in severity. A similar

proportion of subjects in each treatment group had Grade 3 (severe) or 4 (life threatening) laboratory abnormalities (TDF 31.0%; Placebo 37.9%)

The most common Grade 3 or 4 chemistry laboratory AEs that occurred in > 5% of subjects in both treatment groups were increased ALT (TDF: 24.1%, Placebo: 20.7%), and increased aspartate aminotransferase (AST) (TDF: 6.9%, Placebo: 10.3%) groups. In the TDF group, Grade 3 or 4 laboratory AEs reported for > 5% of subjects included Grade 3 increased prothrombin time (5.1%) compared with no subjects in the Placebo group.

In the Placebo group, Grade 3 or 4 laboratory AEs reported for > 5% of subjects included Grade 3 increased amylase (6.9%) and Grade 4 increased potassium (6.9%) compared with no subjects in the TDF group.

8.6.1 Hepatic Laboratory Abnormalities

Graded liver-related laboratory abnormalities included:

- ALT increased (TDF: 41.4%, Placebo: 41.4%), AST increased (TDF: 31%, Placebo: 48.3%), alkaline phosphatase increased (TDF: 13.8, Placebo: 3.4%)
- Total bilirubin increased (TDF: 1.7%, Placebo: 0 subjects)
- INR increased (TDF: 38.5%, Placebo: 30.4%)
- Prothrombin time increased (TDF: 51.3%, Placebo: 43.5%).

Most hepatic laboratory abnormalities were Grade 1 or 2 in severity; Grade 3 or 4 ALT abnormalities and Grade 3 or 4 AST abnormalities were reported for similar percentages of subjects in the TDF and Placebo groups.

8.6.1.1 ALT Flare and Exacerbation of Hepatitis

During the first 48 weeks of double-blind treatment, 5 subjects (8.3%) in the TDF group and 1 subject (3.4%) in the Placebo group (all HBV treatment-naïve) met a predetermined criterion for ALT flare and exacerbation of hepatitis (i.e., ALT > 2 × study baseline and > 10 × ULN, with or without associated symptoms). All of the subjects with ALT flare had graded elevations in ALT at baseline; total bilirubin values remained normal for all subjects with ALT flare; no subjects with ALT flare had increases in HBV DNA; and all remained HBsAg positive. No subjects met a second predetermined criterion for worsening of hepatic function.

8.6.2 Metabolic Laboratory Parameters

Mean (standard deviation [SD]) fasting glucose levels were similar for the TDF (88 mg/dL [10.3 mg/dL]) and Placebo groups (87 mg/dL [8.7 mg/dL]) at baseline. Fasting glucose levels remained stable across the double-blind treatment phase (up to Week 48).

8.6.3 Bone-related Safety Analysis

8.6.3.1 Change in Spine and Whole Body Bone Mineral Density (BMD)

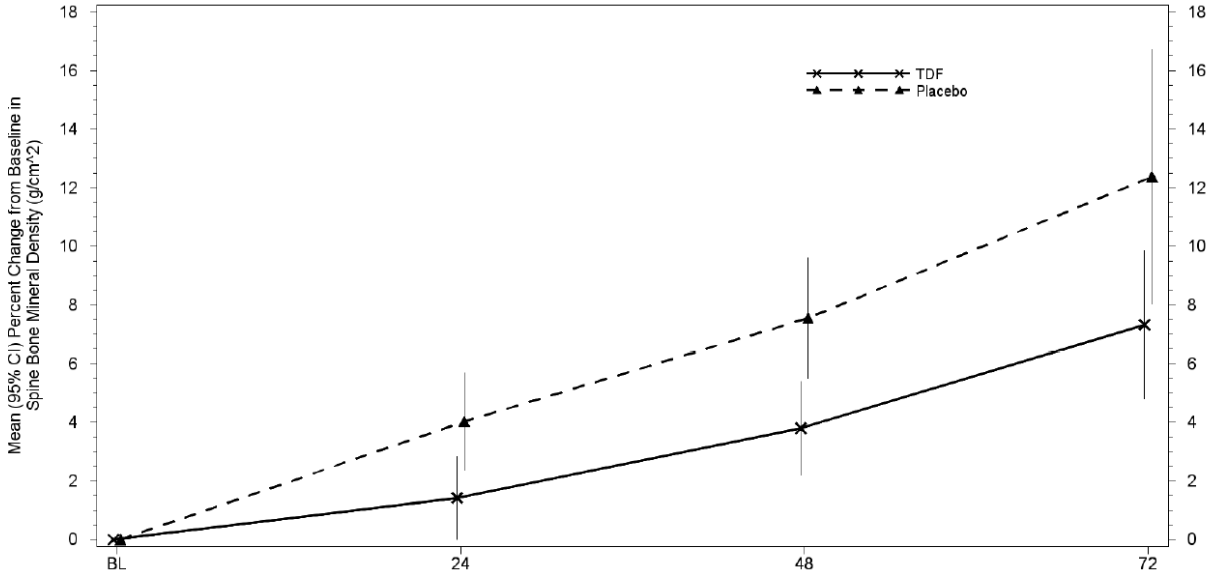
Independent analyses by the FDA Medical Officer were conducted to evaluate the bone-related safety in Study Trial 0144, including the baseline and percent change in Spine and Whole Body BMD from baseline to 24 and 48 weeks of treatment, and the analyses confirmed the findings of the Applicant. Table 4, and Figures 1 and 2 below summarize the mean percent change (Standard deviation, SD) from baseline in Lumbar Spine and Whole Body BMD at Weeks 24 and 48 (Spine and Whole Body DEXA analysis).

Table 4. Percent change from baseline in in Spine and Whole Body Bone Mineral Density at Weeks 24 and 48

	TDF (N = 60)		Placebo (N = 29)		
	N	Mean (SD)	N	Mean (SD)	P-Value
Spine BMD					
Baseline (g/cm^2) [a]	60	0.586 (0.1196)	29	0.626 (0.1567)	0.193
% Change by Week 24 [b]	55	1.426 (5.1997)	28	4.030 (4.2657)	0.025
% Change by Week 48 [c]	55	3.798 (5.9118)	25	7.557 (4.9790)	0.007
Whole Body BMD					
Baseline (g/cm^2) [a]	60	0.565 (0.1086)	29	0.603 (0.1560)	0.177
% Change by Week 24 [b]	55	1.433 (4.0727)	28	4.402 (3.6873)	0.002
% Change by Week 48 [d]	54	4.531 (4.8628)	25	8.883 (5.1210)	<0.001

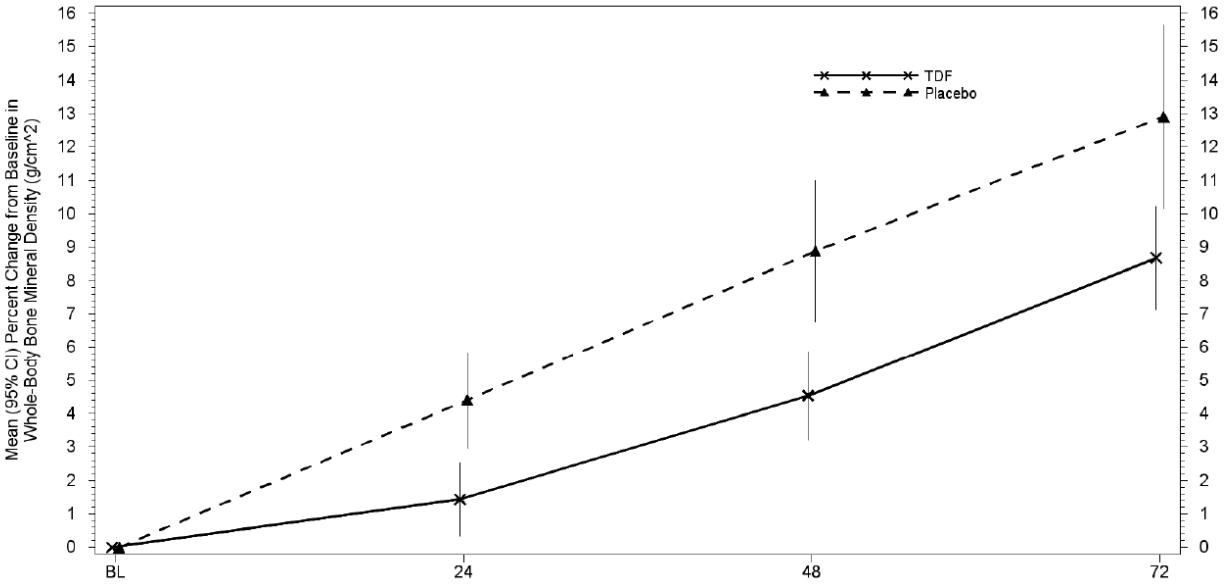
Source: Adapted from Table 25 in Clinical Study Report after verification by independent analysis using the ADBMD (Bone Mineral Density) dataset.
P values were based on a 2-sided Wilcoxon rank sum tests

Figure 1. Percent Change from Baseline in Spine Bone Mineral Density by Visit



Source: Figure 8 and Figure 15.11.12 from Clinical Study Report

Figure 2. Percent Change from Baseline in Whole Body Bone Mineral Density by Visit



Source: Figure 9 and Figure 15.11.13 from Clinical Study Report

Table 5 below summarizes the cumulative incidence of the safety endpoint of ≥ 4% decrease from baseline in Lumbar Spine and Whole Body BMD at Weeks 24 and 48 (Spine and Whole Body DEXA analysis). A higher proportion of subjects in the TDF group had ≥ 4% decrease from baseline in Lumbar Spine and Whole Body BMD at both timepoints as compared to Placebo subjects. This observation is similar to that seen in older HBV pediatric subjects and HIV pediatric subjects exposed to TDF.

Table 5. Percent Change from Baseline and Cumulative Incidence of ≥ 4% Decrease from Baseline in Spine and Whole Body Bone Mineral Density at Weeks 24 and 48

	TDF (N = 60)	Placebo (N = 29)	Proportional difference (95% CI)
Spine BMD			
≥ 4% decrease at Week 24, n/N (%)	10/60 (16.7%)	2/29 (6.9%)	9.8% (−7.7% to 23.2%)
≥ 4% decrease at Week 48, n/N (%)	11/60 (18.3%)	2/29 (6.9%)	11.4% (−6.9% to 25.1%)
Whole Body BMD			
≥ 4% decrease at Week 24, n/N (%)	4/60 (6.7%)	0/29	6.7% (−6.9% to 16.5%)
≥ 4% decrease at Week 48, n/N (%)	4/60 (6.7%)	0/29	6.7% (−6.9% to 16.5%)

Source: Adapted from Table 24 in Clinical Study Report after verification by independent analysis using the ADBMD (Bone Mineral Density) dataset.

8.6.3.2 Change in Lumbar Spine and Whole Body BMD Z-scores

Change in Z-score was also analyzed to see how these children are growing in comparison to healthy children with the same demographic variables. Table 6 below summarizes the percent changes from baseline in BMD Z-scores at Week 48 for subjects with available DEXA data. Lumbar Spine and Whole Body BMD z-scores were

similar at baseline. By Week 48, slight decreases from baseline were observed in the TDF group in both the mean spine and whole body BMD z-scores, and slight increases from the baseline in the Placebo group. However, in both groups, the observed mean and median BMD z-scores values were within the normal range for the population from baseline through 48 weeks of treatment.

Table 6. Percent changes from baseline in BMD Z-scores at Week 48 for subjects with available DEXA data

	TDF (N = 60)	Placebo (N = 29)
Spine BMD Z-score		
Baseline [a]		
Mean (SD)	0.02 (0.977)	−0.29 (1.229)
Median (Q1, Q3)	−0.28 (−0.73, 0.60)	−0.10 (−0.90, 0.48)
Change from Baseline at Week 48 [b]		
Mean (SD)	−0.12 (0.411)	0.14 (0.330)
Median (Q1, Q3)	−0.12 (−0.49, 0.17)	0.11 (−0.06, 0.33)
Whole Body BMD		
Baseline [c]		
Mean (SD)	0.11 (0.743)	−0.05 (1.497)
Median (Q1, Q3)	0.07 (−0.36, 0.68)	0.40 (−0.51, 0.83)
Change from Baseline at Week 48 [d]		
Mean (SD)	−0.18 (0.334)	0.22 (0.446)
Median (Q1, Q3)	−0.22 (−0.41, 0.05)	0.07 (−0.15, 0.56)

Source: Adapted from Table 27 in Clinical Study Report after verification by independent analysis using the ADBMD (Bone Mineral Density) dataset.
[a] TDF: 48 subjects, Placebo = 23 subjects
[b] TDF: 45 subjects, Placebo = 20 subjects
[c] TDF: 17 subjects, Placebo = 12 subjects
[d] TDF: 16 subjects, Placebo = 10 subjects

Most subjects in both treatment groups had spine BMD Z-scores > −1 at baseline and at Week 48. In the TDF group, based on observed data, none of the evaluable subjects had a spine or whole body BMD Z-score < −2 at baseline, and no subjects had a *decrease* in spine or whole body BMD Z-score < −2 at Week 48. However, two subjects with whole body Z-scores < −2 at Week 48 were captured as "missing" at baseline in the shift tables as they did not have whole body Z-scores at baseline. Given the absence of their baseline scores, it is not possible to determine whether they were unchanged, or had an increase or decrease since baseline.

In the Placebo group, 2 subjects had a spine BMD Z-score < −2 and 1 subject had a whole body BMD Z-score < −2 at baseline. BMD Z-score categories improved for these subjects during treatment. One subject in the Placebo group had pituitary dwarfism. At baseline and at each assessment during double-blind treatment, this subject had spine BMD Z-scores < −1 (−1.86 to −1.66) and whole body Z-scores < −2 (−3.59 to −3.05).

8.6.3.3 Bone Laboratory Parameters

Biochemical bone markers in serum and urine were evaluated at baseline and during double-blind treatment. Bone marker values were similar for the TDF and Placebo groups at baseline. During double-blind treatment, bone marker values remained stable, with no between group differences at Week 48, with the exception of the following parameters shown in Table 7. These values indicate increased bone turnover but their clinical significance is not entirely clear.

Table 7. Biochemical bone markers with a significant percent change from baseline

	TDF Median (Q1, Q3) % change from baseline	**Placebo Median (Q1, Q3) % change from baseline**	***P-value****
Fasting phosphate	+3.8% [−2.1%, 11.4%]	−4.3% [−10.5%, 0%]	*p = 0.008*
25-hydroxy Vitamin D	+52.9% [15.6%, 73.8 %]	+16.0% [6.9%, 35.7%]	*p = 0.004*
C-telopeptide	+13.58% [−8.27%, 36.98%]	−7.79 % [−25.44%, 8.00%]	*p = 0.010*

Source: Adapted from Table 30 in Clinical Study Report after verification by independent analysis using the ADBONOUT dataset.
** Wilcoxon rank sum test*

8.6.3.4 Bone-Related Adverse Events

Bone-related AEs were reported in 4 subjects (6.7%) in the TDF group, and in 1 subject (3.4%) in the Placebo group (Table 8).

Table 8. Individual Subjects with Specific Bone-Related Adverse Events

	Subject #	**Age**	**Sex**	**Grade**	**AE**	**SAE**	**Related**	**Drug D/C**	**Spine BMD change**	**Whole Body (WB) BMD change**	**BMD Z-score**
TDF	(b) (6)	7 yr	M	1	Jaw pain + headache	No	No	No	↓	↑	WNL
		7 yr	M	2	Tibia fracture	No	No	No	↑	↓	WNL
		7 yr	M	1	BMD decrease	No	Yes	No	↑	↓	Spine: WNL WB: ↓
		9 yr	M	1	Osteopenia	No	Yes	No	↑	↑	WNL
					Sternum fracture - trauma	No	No				
Placebo		6 yr	M	1	Left arm fracture - fall	No	No	No	↑	↑	WNL

Source: Summarized from text in section "11.2.4.1.1 Bone-related Adverse Events" in Clinical Study Report

The study drug was not interrupted or discontinued for any subject. Two of the AEs were deemed to be related to the study drug (Subjects (b) (6) and (b) (6)). The following is a summarized narrative for each of the 5 subjects:

- Subject (b) (6) was a 7-year-old Asian female in the TDF group, who had a Grade 1, nonserious, pain in jaw and a nonserious headache (Grade 1) on Day 356, which was successfully treated with children's Motrin®. The AEs were assessed as unrelated to the study drug by the investigator; the study

drug was not interrupted or discontinued, and both jaw pain and headache were resolved on Day 371. By the end of double-blind treatment, this subject had an overall decrease from baseline in spine BMD (−2.12%) and an overall increase from baseline in whole body BMD (+2.06%). Spine and whole body BMD Z scores remained within the normal range for age at all time points evaluated.

- Subject (b) (6), was a 7-year-old Asian male in the TDF group, who had a Grade 2, nonserious tibia fracture on Day 14. Whether the fracture was related to trauma was not reported. The subject was treated with antibacterials (amoxicillin, clavulanic acid) ibuprofen, and paracetamol. The AE was assessed as unrelated to the study drug by the investigator; and the study drug was not interrupted or discontinued, and the AE was resolved on Day 98. By the end of double-blind treatment, this subject demonstrated an overall increase from baseline in spine BMD (+6.75%) and an overall decrease from baseline in whole body BMD (−10.13%). Spine and whole body BMD Z scores remained within the normal range for age at all time points evaluated.
- Subject (b) (6), was a 7-year-old Asian male in the TDF group, who had a Grade 1, nonserious BMD decrease on Day 170. The subject was treated with calcium phosphate. The AE was assessed as related to the study drug by the investigator; the study drug was not interrupted or discontinued. At the end of double-blind treatment, this subject demonstrated an overall increase in spine BMD (+8.82%) and an overall decrease in whole body BMD (−9.93%). This subject's spine BMD Z-scores remained within the normal range for age at all time points evaluated; however, whole body BMD Z-scores were below the normal range for age at every time point evaluated (range −2.86 to −3.15).
- Subject (b) (6), was a 9-year-old Asian male in the TDF group, who had a Grade 1, nonserious AE of osteopenia reported on Day 169 that was assessed as related to study drug by the investigator. The subject was treated with risedronate sodium and calcium citrate with cholecalciferol. Study drug was not interrupted or discontinued. Osteopenia was ongoing at the time of the Week 48 data cut. This subject also experienced a Grade 1, nonserious traumatic (per investigator report) fracture of the sternum on Day 836 during the open-label dosing period. The sternum fracture was assessed as unrelated to the study drug by the investigator and was considered resolved on Day 867. At the end of the double-blind treatment, this subject demonstrated overall increases from baseline in spine (+6.47%) and whole body (+7.77%) BMD. Spine and whole body BMD Z-scores were within the normal range for age for the duration of double-blind treatment, with the exception of the spine BMD Z-score at Week 24, which was below the normal range (−2.06).
- Subject (b) (6), was a 6-year-old Asian male in the Placebo group, had a Grade 1, nonserious upper limb fracture (left arm) on Day 2 of double-blind treatment after experiencing a fall. The AE was assessed as unrelated to the study drug by the investigator; the study drug was not interrupted or discontinued, and the AE was considered resolved on Day 58. At the end of the double-blind treatment, this subject demonstrated overall increases from baseline in spine (+5.78%) and whole body (+3.19%) BMD. Spine and whole body BMD Z-scores were within the normal range for age at all time points evaluated.

Medical Officer comment: *For Subject (b) (6), there was no information provided in the Clinical Study Report as to the cause of sternum fracture in this 9 year old child. Given the occurrence of a study-related osteopenia requiring treatment with risedronate sodium and calcium citrate with cholecalciferol, and the rarity of a sternum fracture at this age, the Applicant was asked to provide additional information regarding this subject. The Applicant communicated with the Principal Investigator (PI) at the site who provided additional information that the diagnosis of osteopenia was based on the assessment of a consulted pediatric endocrinologist after reviewing the single DEXA scan reading at Week 24 where the BMD Z-score was below*

the normal range (-2.06). The decision to treat the osteopenia was started on Day 372 (Week 53) despite the increased BMD noted in the Week 48 DEXA scan. The sternal fracture was considered a Grade 1 AE that occurred on Day 836 (Week 120) after the child hit his chest on a shelf or table in his room at home (as per mother). The event was reported to be painless and the subject was followed at a local clinic for a few weeks where it was determined that no treatment was needed (though the ongoing treatment with risedronate sodium and calcium citrate and cholecalciferol may have contributed to the fracture resolution. The study drug was continued unmodified and the AE of sternal fracture resolved on Day 867. The PI has indicated that there is no report of any other known history of fractures or bone injuries in the past.

Medical Officer overall comments on Bone-Related Safety : *While there is no statistical difference between the TDF group and the Placebo group in mean (SD) change over 48 weeks of treatment, or in proportion of subjects with ≥ 4% decrease from baseline in BMD. Children on TDF were less likely to gain BMD than those on Placebo. Data from adult HIV and HBV studies suggest that the TDF effects are most prominent in the first 1-2 years of treatment and then stabilize. In this Study, Body Weight and height do not appear to have been affected during the trial (see Section 8.7.1 below). Long-term data in the HBV 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.*

Because of the lack of long-term data in the HBV pediatric population, and the concern regarding potential long-term effects of TDF exposure on height, overall bone health, and fracture risk we sought other sources of data that may provide some insight into the HBV pediatric population, particularly for the youngest cohort of 2 to 6 years of age. To determine the long-term impact on height and weight in children we reviewed the following two documents:

- **Week 336 Clinical Study Report for Study GS-US-104-0352.** This is "A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy." Although the children were not HBV infected, they received TDF as treatment for ~6.5 years for their HIV infection. Given the increased bone pathology expected from HIV infection, we surmised that if AEs in this cohort were acceptable then we would expect that there would be similar or fewer AEs in HBV-infected children if they were to be treated for a similar duration.
- **A published article identified in a PubMed search**: Giacomet V, Nannini P, Vigano A, Erba P, Benincaso A, Bedogni G, Cattaneo D, Falvella FS, Zuccotti GV. Long-term renal effects of tenofovir-disoproxil-fumarate in vertically HIV-infected children, adolescents, and young adults: a 132-month follow-up study. Clin Drug Investig. 2015 Jul;35(7):419-26. (Giacomet V, 2015) This study evaluated the long-term renal effects of TDF but also evaluated body weight and height. It followed children for 132 months (11 years), of which they received TDF in the last 6 years.

Week 336 Clinical Study Report for Study GS-US-104-0352

Study overview: This was an open-label RCT at 8 study sites: 2 in US, 1 in Panama, 1 in UK. Children 2 to < 16 years currently on HAART and virologically suppressed (HIV-1 RNA < 400 copies/mL) with d4T- or HAART regimens were enrolled. There were two treatment groups: Group 1 who had been previously receiving stavudine (d4T) or zidovudine (ZDV) were switched from these two drugs to TDF plus their other HAART regimen. Group 2 continued their d4T- or ZDV- HAART regimen. This was continued for 48 weeks, after which those in Group 2 were also given TDF. The study enrolled 89 subjects (48 and 41 per each of the two groups) and they were assessed for bone biomarkers at baseline and Weeks 4, 16, 24, 48, 96, 144, 192, and 240.

They also had DEXA scans of lumbar spine and whole body at Weeks 24, 48, and at 24-week intervals through Week 240, then every 48 weeks to measure BMD.

Results: The mean age of enrollment was 8 years (range 2- 15 years). There was considerable attrition and by week 336, only 38 children were still being followed (though only a few dropouts were due to safety issues, most were due to withdrawal of consent). There were no serious safety signals noted through the 6.5 years of follow-up. There were no deaths; 12 (13.5%) had SAEs, none related to study drug, and 9 (10.1%) discontinued the drug due to an AE. Almost all of them had at least 1 AE (n=86, 96.6%), 34 (38.2%) had TEAEs related to the study drug, and 3 (3.4%) had Grade 3 or 4, all related to study drug. Three subjects (3.4%) had bone fractures, but all were trauma-related, and none considered pathological or related to study drug.

Bone Mineral Density (BMD): It was determined that median spine and total body BMD, increased with time. Although there were reductions from baseline in median values for total body Z-scores up to Week 96, they did not progress through Week 336. There were no notable changes from baseline in median values for spine BMD Z-score, overall and by age subgroup (6 to < 12 years and 6 to < 12 years).

Body Weight and Height: At baseline, the children had lower body weight and height for their sex and age (median body weight and height Z-scores were negative at baseline: −0.52 and −0.93, respectively). However, the median body weight and height increased during the study, with a change from baseline by Week 336 in median body weight and height Z-scores of 0.07 and 0.24, respectively. There were AEs where the height was less than normal in one subject; and the weight decreased on 2 subjects. All AEs were considered not related to the study drug.

Summary and conclusions: There were minimal changes in lumbar spine BMD Z-score, which initially showed a modest decline in total body BMD Z-score in the first 2 years that then stabilized out to 6.5 years. The body weight and height for both groups were below normal at baseline, but increased steadily during the study. While there was an initial decline in BMD it stabilized within 2 years and did not seem to affect body weight and height over time. There were bone fractures in 3 subjects, each of which was trauma related and none were considered by the investigator to be pathological or related to the study drug.

Published article by Giacomet et al [Clin Drug Investig. 2015 Jul;35(7):419-26]
This study enrolled 26 vertically HIV-infected patients (13 boys, 13 girls)who were followed every 6 months for 132 months (11 years), of which the last 72 months (6 years) they were treated with TDF. These children were followed for anthropometric parameters (weight, height and BMI), CD4 count, renal function and viral load. All patients received HAART with emtricitabine, lamivudine and PI up to 60 months then HAART with efavirenz, lamivudine and TDF for another 72 months, then followed for a total duration of 132 months.

Results: The mean age of the children at the start of study was 17.3 years (range 10.5 to 23.0 years). Only 3 patients were lost to follow-up. In all patients, weight, height and BMI increased linearly with time. The median increase in weight was from 52.5 to 60 kg, median increase in height was from 157 to 167 cm, and median increase of BMI was from 20 to 21.3 kg/m^2. The CD4+ count and GFR decreased linearly with time (both p>0.01) but were not clinically relevant. The viral load remained undetected throughout follow-up period.

Medical Officer Conclusion: *Overall conclusions from both studies showed that:*

- *Height and weight increased with time in TDF-treated children.*
- *Adjusted height-age Z-scores remained within normal range when compared to CDC growth charts.*
- *Spine BMD Z-scores were minimally affected.*
- *Total Body BMD Z-scores appeared to decrease in the first 2 years then stabilized.*

- *Although the sample size of children 2 to < 6 years was lower than desirable in both studies, they seemed to follow the same trend as the older children.*
- *It is not possible to assess an impact on fractures based on existing studies, but given that BMD Z-scores stabilized after 2 years, this finding is reassuring.*

8.6.4 Renal Safety Parameters

8.6.4.1 Serum creatinine

The mean (SD) serum creatinine levels at baseline were similar for subjects in the TDF (0.40 [0.097] mg/dL]) and Placebo groups (0.43 [0.117] mg/dL). Serum creatinine remained similar to baseline by the end of the 48 Week treatment phase for both groups, with no significant difference between the two groups in the mean (SD) increases from baseline (+0.05 (0.092) mg/dL and +0.01 (0.082) mg/dL, respectively).

8.6.4.2 Estimated Glomerular Filtration Rate (eGFR)

At baseline, the median (Q1, Q3) estimated glomerular filtration rate (eGFR, creatinine clearance [CL_{cr}] using the Schwartz formula) was similar for the TDF and Placebo groups (TDF 167.62 [146.59, 188.26] mL/min/1.72 m^2, Placebo 166.45 [135.74, 187.53] mL/min/1.72 m^2).

For both treatment groups, overall median decreases from baseline in eGFR (CL_{cr}) were observed at Week 16 of double-blind treatment. The median (Q1, Q3) decrease from baseline in eGFR (CL_{cr}) at Week 48 was significantly greater for the TDF group (−8.71 [−27.86, 4.99] mL/min/1.72 m^2) compared with the Placebo group (−0.09 [−14.44, 20.20] mL/min/1.72 m^2); p = 0.047.

8.6.4.3 Renal Abnormalities

During the double-blind treatment phase, 2 subjects in the TDF group (3.3%) and 1 subject in the Placebo group (3.4%) had eGFR (CL_{cr}; using the Schwartz formula) < 70 mL/min/1.73 m^2. The same Placebo subject also had an event of CL_{cr} < 50 mL/min/1.73 m^2

8.6.4.4 Renal Adverse Events

Two subjects in the TDF group had AEs categorized as mild in severity under the system organ class of renal and urinary disorders, including dysuria, hydronephrosis, and pelvic-ureteric obstruction, all were assessed as not related to the study drug.

8.6.4.5 Relationship between Bone Mineral Density and Renal Laboratory Parameters

Analyses were conducted to evaluate the relationships between the following renal laboratory parameters: serum and urine creatinine and phosphate (fasting and nonfasting); calculated eGFR (CL_{cr}) by the Schwartz formula; and renal phosphate threshold, defined as the ratio of renal tubular reabsorption of phosphate (TmP) to eGFR (TmP/GFR) and changes from baseline in spine and whole body BMD at Week 48. Based on an analysis conducted by the FDA biostatistician, we determined that there were no significant differences between the two treatment groups in percent change from baseline in renal phosphate threshold at Weeks 24, 48 and 72, and hence there was no significant correlation between renal phosphate threshold and BMD.

No other consistently significant associations or interactions with treatment were observed for change from baseline in renal parameters and percent change from baseline in spine or whole body BMD at Week 48.

Serum creatinine was positively associated with spine and whole body BMD at baseline and Week 48 when the analysis included all subjects (i.e., across groups) and when the analysis was conducted by treatment group.

Treatment with TDF decreased the magnitude of the positive association between serum creatinine and spine and whole body BMD at Week 48 compared with placebo.

The clinical relevance of these observations is unclear. During 48 weeks of treatment with TDF, changes in BMD did not appear to be clinically related to changes in renal parameters in this population of pediatric CHB subjects.

8.7. Growth

8.7.1 Body Weight and Height

Body weight and height Z-scores were calculated based on the Centers for Disease Control and Prevention (CDC) growth chart. Z-scores are established to compare an individual's weight and height 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 a height or weight that is significantly lower than the norm.

Body weight Z-scores were similar for the TDF and Placebo groups at baseline (Table 9). During the 48 weeks of double-blind treatment, Z-scores decreased slightly for the TDF group and increased slightly for the Placebo group, with mean standard deviation (SD) changes of −0.061 (0.3876) for the TDF group and +0.259 (0.5080) for the Placebo group at Week 48 (*p = 0.005*). Hence, there were no clinically significant changes in weight in the TDF group during the 48 weeks of treatment.

Height Z-scores were similar for the TDF and Placebo groups at baseline (Table 9). During double-blind treatment, Z-scores decreased slightly for both groups, with mean (SD) changes of −0.171 (0.4048) for the TDF group and −0.115 (0.4408) for the Placebo group at Week 48 (p = 0.488), with no clinically or statistically significant change in height in both groups during the 48 weeks of treatment.

Table 9. Changes from Baseline in Mean (SD) Body Weight and Height Z-Scores at Weeks 24 and 48

	TDF (N = 60)		Placebo (N = 29)		
Z-Score	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P-value**
Body Weight					
Baseline	60	−0.213 (1.2357)	29	−0.350 (1.4349)	0.990
% Change by Week 24	57	0.014 (0.3588)	27	0.145 (0.3978)	0.096
% Change by Week 48	55	−0.061 (0.3876)	26	0.259 (0.5080)	0.005
Height					
Baseline	60	0.059 (1.0435)	29	−0.260 (1.3846)	0.549
% Change by Week 24	55	−0.097 (0.2326)	27	−0.078 (0.2949)	0.914
% Change by Week 48	53	−0.171 (0.4048)	26	−0.115 (0.4408)	0.488

Source: Adapted from Table 33 in Clinical Study Report after independent analysis
P values were based on a 2-sided Wilcoxon rank sum tests

8.7.2 Tanner Staging

As expected for the study population of 2 to < 12 year-olds, the majority of males and females in both treatment groups were categorized at Tanner Stage 1 (prepubertal) at enrollment for each category (male genitalia size and lack of pubic hair and female breast size and lack of pubic hair), and most of the subjects remained at Tanner Stage 1 at Week 48

8.8. Special Populations

The pediatric CHB subjects evaluated in Trial 0144 represent a special patient population, and no additional special subgroup analyses were performed, given the low number of subjects that would be included in each subgroup.

8.9. Drug Interactions

No drug interaction studies with TDF have been conducted in pediatric CHB subjects 2 to < 12 years old, since the drug interaction profile of TDF in pediatric CHB patients is not expected to differ from that in CHB adolescents 12 to < 18 years old or adults ≥ 18 years old. No new findings relevant to the coadministration of TDF with other drugs are submitted with this update to the marketing application.

8.10. Use in Pregnancy and Lactation

No notable new findings relevant to use of TDF concomitantly with pregnancy or lactation were submitted with this update to the marketing application. No pregnancies were reported for pediatric CHB subjects in Trial 0144.

9. Advisory Committee Meeting

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

10. Pediatrics

See section 7.0 for discussion regarding efficacy and Section 8.6 for discussion regarding effects on BMD and linear growth.

The Study was reviewed by the Pediatric Review Committee (PeRC) for the pediatric assessment and they agreed with our approval determination and that no additional Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMC) were indicated based on review of the data.

The Study was reviewed and approved for pediatric exclusivity by the Pediatric Exclusivity Board.

11. Other Relevant Regulatory Issues

11.1 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 3 sites, one each in South Korea, Romania and the United States. These sites were selected because they recruited a large proportion of the study population.

Site # 8993: Dr. Jorge Bezerra' site at Cincinnati's Children's Hospital, Cincinnati, Ohio.
Site # 3193: Dr. Daniela Pacurar's site in Bucharest, Romania.
Site # 7118: Dr. Jae Hong Park's site in South Korea.

No regulatory violations were found during inspections at any of these clinical sites. The inspections were classified as No Action Indicated (NAI). The studies were conducted adequately at these three sites, and data from these sites were acceptable to support the validity of the this application. Please refer to the Clinical Inspection Summary from OSI for full details.

11.2 Compliance with Good Clinical Practices

Trial 0144 was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) (Sections 7.6 and 8.2), and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations Title 21, Part 312 (21CFR312)], the European Community Directive 2001/20/EC, and other local legislation.

The appropriate approvals from the independent ethics committee (IEC) or institutional review board (IRB) were secured before study initiation. Protocol amendments and all revisions to the consent form after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

11.3 Financial Disclosures

Gilead Sciences has submitted Form FDA 3454, which certifies that the Applicant (Study 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). There were 42 Principal Investigators and 92 Sub-Investigators, all of whom certified that they have no disclosable financial interests. None of the investigators are Gilead employees. See the Appendix for the Clinical Investigator Financial Disclosure Review Template.

12. Labeling

The USPI and PPI are currently under negotiation; however, the main changes have been agreed to and are summarized below.

Section 2. Dosage and Administration
Sections 2.2 and 2.3 were revised to separate the dosage by formulation, weight and age, instead of only by age. Section 2.2 now describes the TABLET dosage for adults and children 2 years and older and weighing at least 17 kg; and Section 2.3 describes the ORAL POWDER dosage in children for those weighing at least 10 kg.

Section 5.5: Bone Loss and Mineralization Defects

In the 2nd paragraph, last sentence, the following phrase was added, “In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials” to clarify that the existing data only allows us to determine that normal skeletal growth was observed during the clinical trial but that the long-term effect beyond the trial is not known.

The 3rd paragraph was revised as follows:
The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric and adolescent patients, and in particular, the effects of long-duration exposure in younger children, adolescents as well as growing young adults, is unknown.

Section 6.1 Clinical Trials Experience

The Applicant was asked to (b) (6) (Trial 115 and 144) and to summarize the results for both studies in a table. This was done by the Applicant and Table 11 was created with the title "Table 11 Change in Bone Mineral Density from Baseline in Pediatric Subjects 2 Years to <12 Years of Age (Trials 115 and 144)."

Section 8.0 Use in Specific Populations

This section was updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR) format, and text was added to comply with the PLLR format.

Section 8.4 Pediatric Use
This section was simplified to provide a summary of the trials and important efficacy and safety findings and the details of the clinical trials that support the HIV and HBV indication in pediatric patients were moved to Section 14 of the labeling.

Pediatric Patients 2 Years and Older with HIV-1 Infection
The two randomized trials (Trial 352 and Trial 321) in which VIREAD was administered to HIV-infected children aged 2 to < 12 years of age and 12 to < 18 years of age, respectively, were summarized in this section, and the detailed information about these trials was moved to section 14.3 Clinical Trial Results in Pediatric Subjects with HIV-1 Infection.

Also, the following paragraph was added:

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health, and future fracture risk in HIV-1 pediatric patients 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients 2 years and older, and in particular, the effects of long-duration exposure in younger children is unknown *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Pediatric Patients 2 Years of Age and Older with Chronic Hepatitis B
The two randomized trials (Trial 115 and the current study Trial 0144) in which VIREAD was administered to HBV-infected children 12 to < 18 years of age and 2 to < 12 years of age, respectively, were summarized in this section, and the detailed information about these trials was moved to section 14.5 Clinical Trial Results in Pediatric Subjects with Chronic Hepatitis B.

Also, the following paragraph was added:

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health, and future fracture risk in chronic HBV-infected pediatric patients 2 years and older are unknown. The long-term

effect of lower spine and total body BMD on skeletal growth in pediatric patients 2 years and older, and in particular, the effects of long-duration exposure in younger children is unknown [see Warnings and Precautions (5.5), Adverse Reactions (6.1)].

Section 14.1 Overview of Clinical Trials
Four pediatric trials (Trial 352, 321, 115 and 144) were added to Table 19. The clinical data supporting the indications for the pediatric HIV and HBV populations were moved and added, where appropriate, to Section 14.3 and 14.5 as described above.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No recommendation for a REMS is indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are indicated.

14. Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

15. Patient Experience Data

Patient Experience Data is listed in Table 10 below.

Table 10. Patient Experience Data Relevant to this Application (check all that apply)

■	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	■ Clinical outcome assessment (COA) data, such as	-
	□ Patient reported outcome (PRO)	-
	□ Observer reported outcome (ObsRO)	-
	■ Clinician reported outcome (ClinRO)	GS-US-174-0144 Interim 48 Week CSR: • Section 7.5.2.5 Safety Assessments • Section 11.2 Adverse Events • Section 11.4 Serious Adverse Events • Section 11.7 Vital Signs, Physical Findings, and Other Observations Related to Safety
	□ Performance outcome (PerfO)	-
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	-
	□ Patient-focused drug development or other stakeholder meeting summary reports	-
	□ Observational survey studies designed to capture patient experience data	-
	□ Natural history studies	-
	□ Patient preference studies (e.g., submitted studies or scientific publications)	-
	□ Other: (Please specify)	-
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	-
	□ Patient-focused drug development or other stakeholder meeting summary reports	-
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	-
□	Patient experience data was not submitted as part of this application. -	

Source: Submitted by Applicant

References

Giacomet V, N. P. (2015). Long-term renal effects of tenofovir-disoproxil-fumarate in vertically HIV-infected children, adolescents, and young adults: a 132-month follow-up study. . *Clin Drug Investig*, Jul;35(7):419-26.

Terrault NA, L. A. (2018). Update on Prevention, Diagnosis, and Treatment and of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Hepatology*, 67:1560-99.

VIREAD®, G. S. (2017, April). VIREAD® (tenofovir disoproxil fumarate) tablets, for oral use and powder, for oral use. Foster City, CA, U.S.

Appendix

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 021356

Submission Date(s): June 14, 2018

Applicant: Gilead Sciences, Inc.

Product: Tenofovir disoproxil fumarate (Viread)

Reviewer: Samer El-Kamary, MD, MPH

Date of Review: July 16, 2018

Covered Clinical Study (Name and/or Number):
A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection (Study Number: GS-US-174-0144)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 42 Principal Investigators and 92 Sub-Investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The Applicant has adequately disclosed financial interests and has not reported any financial conflicts of interest for Trial 0144: A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection.

[1] See [web address].

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

/s/

SAMER S EL-KAMARY
11/21/2018

WENDY W CARTER
11/21/2018