

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022577Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number: 22577
21356 S-038

Name of Drug: Viread[®] (tenofovir disoproxil fumarate) oral powder
Viread[®] (tenofovir disoproxil fumarate) tablets

Applicant: Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404

Materials Reviewed:

Submission Date: June 16, 2011
December 23, 2011
January 11, 2012
January 13, 2012

Receipt Date: June 16, 2011
December 23, 2011
January 12, 2012
January 17, 2012

Submission Date of Structured Product Labeling (SPL): June 16, 2011

Type of Labeling Reviewed: Word for content and SPL for format.

FDA's November 18, 2011 approved labeling for NDA 21356/S-041 compared to the final draft labeling dated January 13, 2012.

Background and Summary:

This NDA for Viread[®] oral powder (22577) and efficacy supplement for Viread[®] reduced-strength tablets (21356 S-038) were submitted to provide for the use of Viread in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 2 years of age and older.

The labeling in this supplement was compared to the most recent approved labeling dated November 18, 2011.

Review of Package Insert:

General:

The following editorial changes were made throughout the label:

1. Removed the conversion of body weight from kg to pounds (only display weight in kilograms).
2. Capitalized the letter “N” when referring to number of subjects (e.g. N=100).
3. Table numbers were changed throughout the label to accommodate two new tables in Section 2.2 and one new table in Section 12.3.

Highlights Section:

The following changes were made to the drug names at the top of the Highlights section (new wording in blue):

VIREAD® (tenofovir disoproxil fumarate) tablets, for oral use
VIREAD® (tenofovir disoproxil fumarate) powder, for oral use

The following lines were deleted from the Recent Major Changes section:

Indications and Usage (1.1)	09/2011
Indications and Usage (1.2)	10/2010
Dosage and Administration (2.1, 2.2, 2.3)	10/2010

The following lines were added to the Recent Major Changes section:

Indications and Usage (1.1)	01/2012
Dosage and Administration (2.1, 2.2, 2.3)	01/2012
Warnings and Precautions Decreases in Bone Mineral Density (5.6)	01/2012

The following changes were made to the DOSAGE AND ADMINISTRATION section:

Previously read:

-  (b) (4)

Now reads:

- Recommended dose for the treatment of HIV-1 in pediatric patients (2 to less than 18 years of age):
Tablets: for pediatric patients weighing greater than or equal to 17 kg who can swallow an intact tablet, one VIREAD tablet (150, 200, 250 or 300 mg based on body weight) once daily taken orally without regard to food. (2.2)
Oral powder: 8 mg/kg VIREAD oral powder (up to a maximum of 300 mg) once daily with food. (2.2)

The following changes were made to the DOSAGE FORMS AND STRENGTHS section (new wording in blue):

Tablets: 150, 200, 250 and 300 mg (3)

Oral Powder: 40 mg per 1 g of oral powder (3)

The following changes were made to the ADVERSE REACTIONS section (new wording in blue):

In HIV-infected **adult** subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea. (6)

In HIV-infected pediatric subjects: Adverse reactions in pediatric subjects were consistent with those observed in adults. (6)

The following changes were made to the USE IN SPECIFIC POPULATIONS section (deleted wording in strikethrough):

- ~~Pregnancy: There is a pregnancy registry available.~~
- Safety and efficacy not established in patients less than ~~±~~2 years of age. (8.4)

The revision date at the end of the section was revised from November 2011 to January 2012. At the request of DAVP, the revision date was relocated to the bottom of the Highlights page (it was previously located at the top of the Contents page).

Full Prescribing Information: Contents:

The following changes were made to the Table of Contents (new wording in blue, deleted wording in strikethrough):

3.2 Recommended Dose in Pediatric Patients (**2 to Less Than 18** ~~±~~Years of Age ~~and Older and Greater Than or Equal to 35 kg~~)

~~17 PATIENT COUNSELING INFORMATION AND FDA APPROVED PATIENT LABELING~~

Full Prescribing Information:

Section 1.1, Indications and Uses, HIV Infection, the following changes were made (new wording in bold, deleted wording in strikethrough):

VIREAD[®] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients ~~±~~2 years of age and older.

Section 2.1, Recommended Dose in Adults, the following changes were (new wording in bold):

For the treatment of HIV-1 or chronic hepatitis B: The dose is one 300 mg VIREAD tablet once daily taken orally, without regard to food.

For adults unable to swallow VIREAD tablets, the oral powder formulation (7.5 scoops) may be used.

Section 2.2, Recommended Dose in Pediatric Patients (2 to less than 18 Years of Age), the following changes were made (new wording in bold, deleted wording in strikethrough):

For the treatment of HIV-1 in pediatric patients ~~12~~ years of age and older, the recommended oral dose of VIREAD is 8 mg of tenofovir disoproxil fumarate per kilogram of ~~with~~ body weight (up to a maximum of ~~greater than or equal to 35 kg (greater than or equal to 77 lb): The dose is one~~ 300 mg) once daily administered as oral powder or tablets.

VIREAD oral powder should be measured only with the supplied dosing scoop. One level scoop delivers 1 g of powder which contains 40 mg of tenofovir disoproxil fumarate. VIREAD oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, yogurt). The entire mixture should be ingested immediately to avoid a bitter taste. Do not administer VIREAD oral powder in a liquid as the powder may float on top of the liquid even after stirring. Further patient instructions on how to administer VIREAD oral powder with the supplied dosing scoop are provided in the FDA-approved patient labeling (Patient Information).

VIREAD is also available as tablets in 150, 200, 250 and 300 mg strengths for pediatric patients who weigh greater than or equal to 17 kg and who are able to reliably swallow intact tablets. The dose is one tablet once daily taken orally, without regard to food.

Tables 1 and 2 contain dosing recommendations for VIREAD oral powder and tablets based on body weight. Weight should be monitored periodically and the VIREAD dose adjusted accordingly.

Table 1 Dosing Recommendations for Pediatric Patients ≥ 2 Years of Age Using VIREAD Oral Powder

Body Weight Kilogram (kg)	Oral Powder Once Daily Scoops of Powder
10 to <12	2
12 to <14	2.5
14 to <17	3
17 to <19	3.5
19 to <22	4
22 to <24	4.5
24 to <27	5
27 to <29	5.5
29 to <32	6
32 to <34	6.5
34 to <35	7
≥ 35	7.5

Table 2 Dosing Recommendations for Pediatric Patients ≥ 2 Years of Age and Weighing ≥ 17 kg Using VIREAD Tablets

Body Weight Kilogram (kg)	Tablets Once Daily
17 to <22	150 mg
22 to <28	200 mg
28 to <35	250 mg
≥ 35	300 mg

Section 2.3, Dose Adjustment for Renal Impairment in Adults, the following changes were made (new wording in blue, deleted wording in strikethrough):

Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment [See *Clinical Pharmacology (12.3)*]. Therefore, the dosing interval of VIREAD tablets 300 mg should be adjusted in patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table 3.1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval

adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients [See *Warnings and Precautions (5.3)*]. There are no data to recommend use of VIREAD tablets 150, 200 or 250 mg or VIREAD oral powder in patients with renal impairment.

No dose adjustment of VIREAD tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment [See *Warnings and Precautions (5.3)*].

No data are available to make dose recommendations in pediatric patients ~~12 years of age and older~~ with renal impairment.

Section 3, DOSAGE FORMS AND STRENGTHS, the following changes were made (new wording in blue, deleted wording in strikethrough):

VIREAD is available as tablets or as an oral powder.

VIREAD tablets 150 mg contain 150 mg of tenofovir disoproxil fumarate, which is equivalent to 123 mg of tenofovir disoproxil. The tablets are triangle-shaped, white, film-coated, and debossed with “GSI” on one side and “150” on the other side.

VIREAD tablets 200 mg contain 200 mg of tenofovir disoproxil fumarate, which is equivalent to 163 mg of tenofovir disoproxil. The tablets are round-shaped, white, film-coated, and debossed with “GSI” on one side and “200” on the other side.

VIREAD tablets 250 mg contain 250 mg of tenofovir disoproxil fumarate, which is equivalent to 204 mg of tenofovir disoproxil. The tablets are capsule-shaped, white, film-coated, and debossed with “GSI” on one side and “250” on the other side.

VIREAD tablets 300 mg contain ~~—Each tablet contains~~ 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, and debossed with “GILEAD” and “4331” on one side and with “300” on the other side.

The oral powder consists of white, taste-masked, coated granules containing 40 mg of tenofovir disoproxil fumarate, which is equivalent to 33 mg of tenofovir disoproxil, per level scoop. Each level scoop contains 1 gram of oral powder.

Section 5.6, Decreases in Bone Mineral Density, the following changes were made (new wording in blue, deleted wording in strikethrough):

Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients ~~12 years of age and older~~ who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

In a clinical trials evaluating VIREAD in ~~trial of~~ HIV-1 infected pediatric subjects 2 to less than 18 ~~12~~ years of age and older (Study 321), bone effects were similar to those observed in adult subjects. Under normal circumstances BMD increases rapidly in pediatric patients. ~~this age group.~~ In Study 352 (2 to less than 12 years) ~~this trial,~~ the mean rate of BMD ~~bone~~ gain in lumbar spine at Week 48 was similar between ~~less in~~ the VIREAD and the d4T or AZT treatment groups. Total body BMD gain was less in the VIREAD compared to the d4T or AZT treatment group. One VIREAD-treated subject and none of the d4T or AZT ~~group compared to the placebo group.~~ Six VIREAD-treated subjects experienced ~~and one placebo treated subject had~~ significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD ~~weeks.~~ Among 28 subjects receiving 96 weeks of VIREAD, Z-scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with VIREAD for 96 weeks. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the VIREAD compared to the placebo treatment group. Six VIREAD treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were ~~declined by~~ -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with VIREAD for 96 weeks. In both trials, ~~skeletal.~~ Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects ~~12 years of age and older~~ suggest increased bone turnover, consistent with the effects observed in adults.

Section 6.1, Adverse Reactions from Clinical Trials Experience, under *Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection*, the following changes were made (new wording in blue, deleted wording in strikethrough):

Clinical Trials in Pediatric Subjects ~~12~~ Years of Age and Older with HIV-1 Infection

Assessment of adverse reactions is based on ~~two one~~ randomized trials (Studies 352 and ~~trial (Study 321)~~ in 184 ~~87~~ HIV-1 infected pediatric subjects (~~12~~ to less than 18 years of age) who received treatment with VIREAD (N=93 ~~45~~) or placebo/~~active comparator~~ (N=91 ~~42~~) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in subjects who received treatment with VIREAD were consistent with those observed in clinical trials in adults.

Bone effects observed in pediatric subjects ~~12~~ years of age and older were consistent with those observed in adult clinical trials [*See Warnings and Precautions(5.6)*].

Eighty-nine pediatric subjects received VIREAD in Study 352 (48 who were initially randomized to VIREAD and 41 who were initially randomized to continue stavudine or zidovudine and then received VIREAD in the extension phase) for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score [*See Warnings and Precautions (5.6)*].

Section 8.3, Nursing Mothers, the following changes were made (new wording in blue, deleted wording in strikethrough):

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. **In humans, samples**

of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that ~~It is not known whether~~ tenofovir is excreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.**

Section 8.4, Pediatric Use, the following changes were made (new wording in blue, deleted wording in strikethrough):

The safety of VIREAD in pediatric patients aged ~~12~~ to less than 18 years is supported by data from ~~two one~~ randomized trials in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In addition ~~this trial~~, the pharmacokinetic profile of tenofovir in patients 2 to less than 18 years of age at the recommended doses ~~VIREAD~~ was similar to that found to be safe and effective in adult clinical trials [See *Clinical Pharmacology (12.3)*].

In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with VIREAD (N = 44) or continue their original regimen (N = 48) for 48 weeks. Five additional subjects over the age of 12 were enrolled and randomized (VIREAD N=4, original regimen N=1) but are not included in the efficacy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label VIREAD. At Week 48, 89% of subjects in the VIREAD treatment group and 90% of subjects in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations less than 400 copies/mL. During the 48 week randomized phase of the study, 1 subject in the VIREAD group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the VIREAD group and 1 subject in the stavudine or zidovudine group) discontinued for other reasons.

Safety and effectiveness of VIREAD in pediatric patients younger ~~less~~ than ~~12~~ years of age have not been established.

Section 11, DESCRIPTION, the following changes were made (new wording in blue, deleted wording in strikethrough):

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~~. ~~Each tablet contains 300 mg of tenofovir disoproxil fumarate, which are is-equivalent to 123, 163, 204 and 245 mg of tenofovir disoproxil, respectively. Each tablet contains and~~ the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The 300 mg tablets are coated with Opadry II Y-30-10671-A, which contains FD&C blue #2 aluminum lake, hypromellose hydroxypropyl ~~hydroxypropyl methylcellulose~~ 2910, lactose monohydrate, titanium dioxide, and triacetin. The 150, 200, and 250 mg tablets are coated with Opadry II 32K-18425, which contains hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

VIREAD oral powder is available for oral administration as white, taste-masked, coated granules containing 40 mg of tenofovir disoproxil fumarate 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.

Section 12.3, Pharmacokinetics, under *Absorption*, the following changes were made (new wording in blue):

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Section 12.3, Pharmacokinetics, under *Effects of Food on Oral Absorption*, the following changes were made (new wording in blue):

Administration of VIREAD 300 mg tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of VIREAD with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are $0.33 \pm 0.12 \mu\text{g/mL}$ and $3.32 \pm 1.37 \mu\text{g}\cdot\text{hr/mL}$ following multiple doses of VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Section 12.3, Pharmacokinetics, under *Special Populations*, the following changes were made (new wording in blue, deleted wording in strikethrough):

Pediatric Patients ~~12~~ Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 ~~8~~-HIV-1 infected pediatric subjects (~~12~~ to less than 18 years (Table 11)). Mean (\pm SD) C_{max} and AUC_{tau} are $0.38 \pm 0.13 \mu\text{g/mL}$ and $3.39 \pm 1.22 \mu\text{g}\cdot\text{hr/mL}$, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral once daily doses of VIREAD 300 mg (tablet) or 8 mg/kg of body weight (powder) up to a maximum dose of 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Table 11 Mean (\pm SD) Tenofovir Pharmacokinetic Parameters by Age Groups for Pediatric Patients

Dose and Formulation	300 mg Tablet	8 mg/kg Oral Powder
	12 to <18 Year (N=8)	2 to <12 Years (N=23)
C_{max} ($\mu\text{g/mL}$)	0.38 ± 0.13	0.24 ± 0.13
AUC_{tau} ($\mu\text{g}\cdot\text{hr/mL}$)	3.39 ± 1.22	2.59 ± 1.06

~~Pharmacokinetic trials have not been performed in pediatric subjects under 12 years of age.~~

Section 16, HOW SUPPLIED/STORAGE AND HANDLING, the following changes were made to (new wording in blue, deleted wording in strikethrough):

VIREAD was studied in a small randomized, double-blind, active-controlled trial evaluating the safety of VIREAD compared to other antiviral drugs in subjects with CHB and decompensated liver disease through 48 weeks (Study 0108).

Forty-five adult subjects (37 males and 8 females) were randomized to the VIREAD treatment arm. At baseline, 69% subjects were HBeAg-~~negative~~ ~~positive~~, and 31% were HBeAg-~~positive~~ ~~negative~~. Subjects had a mean Child-Pugh score of 7, a mean MELD score of 12, mean HBV DNA of 5.8 log₁₀ copies/mL and mean serum ALT of 61 U/L at baseline. Trial endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine \geq 0.5 mg/dL or confirmed serum phosphorus of $<$ 2 mg/dL. [See Adverse Reactions (6.1)].

Section 12.3, Pharmacokinetics, under *Special Populations*, the following changes were made (new wording in blue, deleted wording in strikethrough):

Tablets

VIREAD tablets, 150 mg, are ~~triangle~~ ~~The almond-shaped, white~~ ~~light blue~~, film-coated tablets containing 150 ~~contain 300~~-mg of tenofovir disoproxil fumarate, which is equivalent to 123 ~~245~~-mg of tenofovir disoproxil, are debossed with “GSI GILEAD” and “4331” on one side and with “150 ~~300~~” on the other side. Each bottle contains 30 tablets, ~~and are available in unit of use bottles (containing a desiccant (silica gel canister or sachet),]~~ and closed with a child-resistant closure. ~~)-of: 30 tablets (NDC 61958-0404--0404-1)~~

VIREAD tablets, 200 mg, are round-shaped, white, film-coated tablets containing 200 mg of tenofovir disoproxil fumarate, which is equivalent to 163 mg of tenofovir disoproxil, are debossed with “GSI” on one side and with “200” on the other side. Each bottle contains 30 tablets, a desiccant (silica gel canister or sachet), and closed with a child-resistant closure. (NDC 61958-0405-1)

VIREAD tablets, 250 mg, are capsule-shaped, white, film-coated tablets containing 250 mg of tenofovir disoproxil fumarate, which is equivalent to 204 mg of tenofovir disoproxil, are debossed with “GSI” on one side and with “250” on the other side. Each bottle contains 30 tablets, a desiccant (silica gel canister or sachet), and closed with a child-resistant closure. (NDC 61958-0406-1)

VIREAD tablets, 300 mg, are almond-shaped, light blue, film-coated tablets containing 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, are debossed with “GILEAD” and “4331” on one side and with “300” on the other side. Each bottle contains 30 tablets, a desiccant (silica gel canister or sachet), and closed with a child-resistant closure. (NDC 61958-0401-1)

Oral Powder

VIREAD oral powder consists of white, coated granules containing 40 mg of tenofovir disoproxil fumarate, which is equivalent to 33 mg of tenofovir disoproxil, per gram of powder and is available in multi-use bottles containing 60 grams of oral powder, closed with a child-resistant closure, and co-packaged with a dosing scoop. (NDC 61958-0403-1)

Store VIREAD tablets and oral powder at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Keep the bottle tightly closed. Dispense only in original container. Do not use if seal over bottle opening is broken or missing.

Section 17, Patient Counseling Information, the following changes were made immediately below the section heading (new wording in blue, deleted wording in strikethrough):

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Section 17, Patient Counseling Information, Information for Patients, the following changes were made (new wording in blue, deleted wording in strikethrough):

- Patients should avoid doing things that can spread HIV or HBV to others.
- Do not share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes
~~The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and razor blades.~~
- Do not have any kind of sex without protection. Always practice safe sex by using a ~~to use~~ latex or polyurethane ~~condoms~~ condom ~~condoms~~ to lower the chance of sexual contact with ~~any body fluids such as semen, vaginal secretions, or blood. Patients should be advised never to re-use or share needles.~~
- Do not breastfeed. Tenofovir is excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- The long term effects of VIREAD are unknown.
- VIREAD ~~tablets and oral powder~~ ~~Tablets~~ are for oral ingestion only.

Section 17, Patient Counseling Information, the following changes were made:

The warnings/precautions listed were rearranged to follow the order in Warnings and Precautions section of the PI (in numerical order: 5.1, 5.2, 5.3, 5.4, 5.5, 5.6).

Review of Patient Package Insert:

In the heading of the PPI, the following changes were made (new wording in blue, deleted wording in strikethrough):

PATIENT INFORMATION
VIREAD® (VEER-ee-ad)
(tenofovir disoproxil fumarate)
tablets and oral powder ~~Tablets~~

In the first paragraph of the PPI, the following changes were made (new wording in blue, deleted wording in strikethrough):

Read this **Patient Information** ~~leaflet~~ before you start taking VIREAD and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or **your** treatment.

In the section, “What is the most important information I should know about VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

1. Build-up of an acid in your blood (lactic acidosis). Lactic acidosis can happen in some people who take VIREAD ~~or similar (nucleoside analog) medicines~~. **Lactic acidosis** is a serious medical emergency that can lead to death.

2. Severe liver problems. Severe liver problems can happen in people who take VIREAD ~~or similar medicines~~. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take VIREAD.

Call your healthcare provider right away if you have any of the following symptoms of liver problems:

- Your skin or the white part of your eyes turns yellow (jaundice).
- dark “tea-colored” urine
- light-colored ~~bowel~~ **bowel** movements (stools)
- loss of appetite for several days or longer
- nausea
- stomach pain

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking VIREAD ~~or a similar medicine~~ for a long time.

3. Worsening of your Hepatitis B infection. Your hepatitis B Virus (HBV) infection may become worse (flare-up) if you take VIREAD and then stop it. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.

- Do not let your VIREAD run out. Refill your prescription or talk to your healthcare provider before your VIREAD is all gone.
- Do not stop taking VIREAD without first talking to your healthcare provider.
- If you stop taking VIREAD, your healthcare provider will need to check your health often and do ~~regular~~ blood tests **regularly** to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking VIREAD.

In the section “What is VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

VIREAD is a prescription medicine used:

- with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in adults and ~~children pediatric patients~~ **12 years of age and older**. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
 - When used with other HIV medicines, VIREAD may reduce the amount of HIV in your blood (called “viral load”). VIREAD may also help to increase the number of CD4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

- **VIREAD does not cure HIV infection or AIDS.** People taking VIREAD may still develop infections or other conditions associated with HIV infection.
- Patients must stay on continuous HIV therapy to control infection and decrease HIV-related illnesses.
- ~~VIREAD does not cure HIV or AIDS. People taking VIREAD may still get infections common in people with HIV (opportunistic infections).~~ It is very important that you stay under the care of your healthcare provider.
- to treat chronic hepatitis B virus (HBV) in adults. VIREAD will not cure HBV.
 - VIREAD may lower the amount of HBV in your body.
 - VIREAD may improve the condition of your liver.
 - ~~VIREAD may lower the ability of HBV to multiply and infect new liver cells.~~

In the section “What should I tell my healthcare provider before taking VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

Do not breastfeed if you are taking VIREAD. ~~Tenofovir passes into your breast milk.~~ ~~are breast feeding or plan to breast feed.~~ You should not breastfeed ~~because of the risk of passing~~ ~~feed if you have HIV infection or AIDS.~~ ~~The virus that causes HIV can pass through your breast milk to your baby. It is not known if VIREAD can pass through your breast milk and harm your baby.~~ Talk to your healthcare provider about the best way to feed your baby.

In the section “How should I take VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

- **For adults:** ~~the~~ The usual dose of VIREAD is **one 300 mg±** tablet each day. If you ~~are an adult~~ ~~and~~ have kidney problems, your healthcare provider may tell you to take VIREAD less often.
- **Adults who are unable to swallow VIREAD tablets whole may take 7½ scoops of VIREAD oral powder.**
- **For children 2 years of age and older, your healthcare provider will prescribe the right dose of VIREAD oral powder or tablets based on your child’s body weight.**
- **Tell your healthcare provider if your child has problems with swallowing tablets.**
- **See the “Instructions for Use” section at the end of this Patient Information leaflet for information about the right way to measure and take VIREAD oral powder.**
- **Take VIREAD tablets by mouth, with or without food.**

In the section “What are the possible side effects of VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough). *Note that above the first table, the order of words is incorrect and should state “in all” instead of “all in.”*

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your **healthcare provider** ~~doctor~~ if you start having new symptoms after starting your HIV medicine.
The most common side effects **in all people who take** ~~of~~ VIREAD are:

- nausea
- rash
- diarrhea
- headache
- pain
- depression
- weakness

In some people with advanced HBV-infection, other common side effects may include:

- sleeping problems
- itching
- vomiting
- dizziness
- fever

In the section “How should I store VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

How should I store VIREAD?

- Store VIREAD tablets or oral powder at 59° F to 86° F (15° C to 30° C).
- Keep VIREAD in the original container.
- Do not use VIREAD if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed.

In the section “General information about VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VIREAD for a condition for which it was not prescribed. Do not give VIREAD to other people, even if they have the same condition you have. It may harm them.

Avoid doing things that can spread VIREAD does not reduce the risk of passing HIV-1 or HBV infection to others.

- **Do not share needles** through sexual contact **or other injection equipment.**
- ~~blood contamination. Continue to practice safer sex and do not use or share dirty needles.~~
Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

A ~~shot~~(vaccine) is available to protect people at risk for becoming infected with HBV. You can ask your healthcare provider for information about this vaccine.

In the section “What are the ingredients in VIREAD?” the following changes were made (new wording in blue, deleted wording in strikethrough):

Oral Powder: mannitol, hydroxypropyl cellulose, ethylcellulose, and silicon dioxide.

Tablets: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

Tablet Coating:

VIREAD tablets 300 mg: Opadry II Y-30-10671-A, which contains FD&C blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

VIREAD tablets 150, 200 and 250 mg: Opadry II 32K-18425, which contains hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

The entire section “Instructions for Use of VIREAD oral powder” was added, as copied below:

Instructions for Use of VIREAD oral powder

Read the Instructions for Use below before you give VIREAD oral powder. Be sure you can understand and follow them. If you have any questions, ask your healthcare provider or pharmacist.

Important information

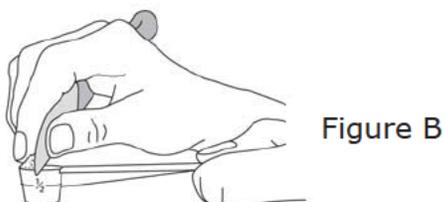
- VIREAD oral powder comes in a box that has a bottle of VIREAD and a dosing scoop (see Figure A).



- **Only use the dosing scoop to measure VIREAD oral powder.**
- **Only mix VIREAD oral powder with soft foods** that can be swallowed without chewing. Examples of soft foods you can use are: applesauce, baby food, or yogurt.
- **Do not mix VIREAD oral powder with liquid.** The powder may float to the top even after stirring.
- **Give the entire dose right away after mixing** to avoid a bad taste.

How do I prepare and give VIREAD oral powder?

1. Wash and dry your hands.
2. Measure $\frac{1}{4}$ to $\frac{1}{2}$ cup of soft food into a cup or bowl.
3. To open a new bottle of powder, press down on the bottle lid and turn to remove (see picture on the top of the bottle cap). Peel off the foil.
4. Measure the number of scoops prescribed by your healthcare provider.
 - For each full scoop prescribed:
 - Fill the dosing scoop to the top.
 - Use the flat edge of clean knife to make the powder even with the top of the scoop (see Figure B).



- For ½ scoop:
 - Fill the dosing scoop up to the “½ line” on the side (see Figure C).

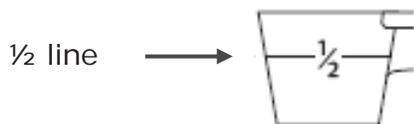


Figure C

5. Sprinkle the VIREAD oral powder on the soft food. Stir with a spoon until well mixed. **Give the entire dose right away after mixing** to avoid a bad taste.
6. Close the bottle of VIREAD tightly.
7. Wash and dry the dosing scoop. Do not store the dosing scoop in the bottle.

See the section “How should I store VIREAD?” for information about how to store VIREAD oral powder.

At the end of the PPI, the following changes were made (new wording in blue, deleted wording in strikethrough):

[This Patient Information has been approved by the U.S. Food and Drug Administration.](#)

~~November 2011~~

~~COMPLERA, EMTRIVA, HEPSERA, TRUVADA, and VIREAD are trademarks or registered trademarks of Gilead Sciences, Inc., or its related companies. ATRIPLA is a trademark of Bristol Myers Squibb & Gilead Sciences, LLC. All other trademarks herein are the property of their respective owners.~~

Manufactured for and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

[January 2012](#)

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[21-356-DGS-030 11012012](#)

Conclusion:

It will be conveyed to the applicant that labeling is acceptable, and an approval letter should be sent. See the clinical review for additional information.

[\[See appended electronic signature page\]](#)

Katherine Schumann
Regulatory Project Manager

Supervisory Comment/Concurrence:

{See appended electronic signature page}

Victoria Tyson
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachments: PI and PPI submitted by Gilead on January 13, 2012, compared to the last approved label on November 18, 2011.

Drafted: RPM/Schumann/1-12-12
Revised/Initialed: Tyson/eso/
Finalized: RPM/Schumann/
Filename:v: \\Cdsnas\oap\DAVDP\CSO\Schumann\NDA\022477\RPM labeling review 22577
21356 S-38.doc

48 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

KATHERINE SCHUMANN
01/18/2012

VICTORIA L TYSON
01/18/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 22577

PMR/PMC Description: 1865-1 During the filling of one commercial full-scale Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report.

PMR/PMC Schedule Milestones:

Study/Trial Completion:	<u>12/18/2012</u>
Final Report Submission:	<u>01/18/2013</u>
Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data presented to date demonstrates adequate uniformity of strength. However, non-uniform strength per gram as a function of particle size makes it possible that segregation during shipping and/or during the packaging operation could cause strength to vary from bottle to bottle. This concern makes it important to obtain additional data from a commercial full-scale batch of the oral powder.

The submitted pediatric clinical trial supports use of this formulation in patients 2-12 years of age for over 1 year of dosing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The potential for variation of strength from one bottle to another during the filling process is the issue, and the goal of the study is to demonstrate that this does not occur during commercial full-scale manufacture.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A CMC study will be conducted to confirm that the bulk powder blend does not segregate during shipping or during final packaging, which could theoretically lead to varied strength from one bottle to another. PMC Language: "During the filling of one commercial full-scale Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report."

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Quality study for dose uniformity

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

KATHERINE SCHUMANN
01/18/2012

RAPTI D MADURawe
01/18/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 22577

PMR/PMC Description: 1865-2 Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient. Include data from each scoop sampled and appropriate statistical analysis in the study report.

PMR/PMC Schedule Milestones:

Study/Trial Completion:	<u>12/18/2012</u>
Final Report Submission:	<u>01/18/2013</u>
Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data presented to date demonstrates adequate uniformity of strength. However, non-uniform strength per gram as a function of particle size makes it possible that segregation could occur within the container prior to receipt by the patient or as the care-giver measures out doses. This could cause the strength to vary dose by dose. This concern makes it important to obtain additional data from a simulated in-use study.

The submitted pediatric clinical trial supports use of this formulation in patients 2-12 years of age for over 1 year of dosing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The potential for variation of strength from dose to dose is the issue, and the goal of the study is to demonstrate that this does not occur during shipment prior to patient receipt or during dosing.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A CMC study will be conducted to confirm that the powder blend in the commercial container does not segregate during shipping to the patient or during dosing, which could theoretically lead to varied strength from one one dose to another.
PMC Language: "Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient. Include data from each scoop sampled and appropriate statistical analysis in the study report."

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Quality study for dose uniformity
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

KATHERINE SCHUMANN
01/18/2012

RAPTI D MADURawe
01/18/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 19, 2011

TO: Debra B. Birnkrant, M.D., Director,
Division of Antiviral Drug Products (DAVP)

John Lazor, Pharm.D., Director,
Division of Clinical Pharmacology 4 (DCP4)

FROM: Arindam Dasgupta, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-577, VIREAD® (tenofovir disoproxil fumarate) Oral Powder, 300 mg sponsored by Gilead Sciences, Inc.

At the request of Division of Antiviral Drug Products (DAVP) and Division of Clinical Pharmacology 4 (DCP4), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an inspection of the clinical and analytical portions of the following bioequivalence studies:

Study GS-US-104-0312: "A Phase I Pharmacokinetic Study to Evaluate the Relative Bioavailability and Bioequivalence Between Tenofovir Disoproxil Fumarate (Tenofovir DF) Oral Powder and Tablet Formulations"

Study GS-US-104-0352: "A Phase 3, 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"

The audits of the clinical and analytical portions of the studies were conducted at Comprehensive Clinical Development, Tacoma, WA (clinical site #1), Hospital del Niño Infectology Service, Panama City, PANAMA (clinical site #2) and at Gilead Sciences, Inc., Foster City, CA (analytical site). Following the audit at the clinical site #2 in Panama City, PANAMA (November 7-11, 2011), no significant objectionable conditions were observed and Form FDA-483 was not issued. Following inspections of the clinical site #1 (October 24-31, 2011) and analytical site, Form FDA-483 was issued at each site (Attachments 1 and 2). DBGC received Comprehensive Clinical Development's written response (dated November 14, 2011) to the inspectional findings on November 15, 2011 (Attachment 3). Please note that DBGC is yet to receive written response to the inspectional findings from Gilead Sciences. We will amend this memorandum if the response changes our conclusion. The Form FDA-483 observations and our evaluations of the observations follow.

Clinical Site #1: Comprehensive Clinical Development, Tacoma, WA

1. An investigation was not conducted in accordance with the investigational plan. Specifically, adequate accountability records of all unused study drug were not maintained by the pharmacy. For example, the documents pertaining to the storage of the bio-retention samples used in the study were incorrect and included erroneous information including the following:
 - The lot number of the test article was listed as A13768A and should have been AD501A1.
 - Two of the dates of inventory listed on the document precede the receipt of the test article.
 - The amount of the empty bottles on hand was incorrect and was listed as 15 empty bottles when there were 30 empty bottles of the test article.
 - The document has not been reviewed by the pharmacy manager.

In their response, Comprehensive Clinical Development acknowledged the above observation and indicated that they were documentation errors which resulted from erroneous information being "cut and pasted" into the source logs from another study conducted around the same time. Further, at the time when the study was conducted, the logs were not being reviewed by the Pharmaceutical Services Director for accuracy. Since the acquisition of the firm in March 2011, Comprehensive Clinical

Development conducted an internal investigation and initiated corrective and preventive actions to prevent similar occurrences in future studies.

However, during the inspection, lot numbers for reserve samples were physically verified and dosing logs were checked to confirm that each subject received the correct formulations during dosing. Hence the above observation is not likely to affect study outcomes.

Analytical Site: Gilead Sciences, Inc., Durham, NC
(audited at Gilead Sciences, Foster City, CA)

- 1. Failure to conduct a re-injection reproducibility experiment during pre-study method validation for tenofovir LC-MS/MS method. Samples for subjects 20 and 21 were re-injected multiple times in Gilead study GS-US-104-0312. The original chromatograms were not maintained with the study documentation.**

The accuracy of pharmacokinetic measurements for subjects 20 and 21 (in study **GS-US-104-0312**) is not assured as reinjection reproducibility was not demonstrated during pre-study method validation. Because the Gilead facility in Durham has closed, it is not possible to perform a retrospective validation of HPLC re-injection reproducibility under the conditions of the study. Because the original chromatograms are not available for audit, the analytical operations cannot be reconstructed for evaluation. Hence data for subjects 20 and 21 should be excluded from the bioequivalence assessment.

- 2. Failure to document all aspects of study conduct. For example:**
 - a. The storage location for processed samples in Gilead study number GS-US-104-0312 was not documented. As the storage location and conditions can not be confirmed by documentation, the integrity of the processed samples prior to injection into the LC/MS/MS can not be assured.**

Gilead's records did not document processing start and end times or the storage location for processed samples prior to injection. Samples from multiple subjects (up to 8 subjects, 96 samples/subject) were processed on the same day by the same analyst. In absence of documentation on interim storage prior to injection, the integrity of the processed samples cannot be confirmed. However, the analyst processed matrix-based

calibrators and quality control (QC) samples together with the study samples.

While the documentation is incomplete, the data from calibrator and QC samples confirm that the extracts of processed samples were sufficiently stable during the actual times and conditions of storage.

- b. Failure to maintain documentation for individual calibrators and QC sets used during sample processing for Gilead study GS-US-104-0312.
- c. The plate position of samples loaded onto the 96 well plates for Gilead Studies GS-US-104-0312 and GS-US-104-0352 were not documented.
- d. There was no documentation to confirm that the autosampler injection sequence was verified in Gilead Studies GS-US-104-0312 and GS-US-104-0352
- e. Tomtec program used during subject sample analysis for Gilead studies GS-US-104-0312 and GS-US-104-0352 was not documented.
- f. The firm did not maintain the record of receipt and storage for reference materials used during method validation.
- g. Lack of objective criteria established a priori for re-assays. For example, samples from subject 5 and 24 in Gilead study GS-US-104-0312 were repeated due to "initial questionable results."

Concerning observations 2b-2g, Gilead did not maintain source records or documentation for the activities related to studies GS-US-104-0312 and GS-US-104-0352. Observations 2b-2g are not likely to affect the acceptability of the reported data.

Conclusion:

Following the above inspections, DBGCC recommends that the data from the clinical portion of studies -US-104-0312 and GS-US-104-0352 can be accepted for Agency review.

The accuracy of pharmacokinetic measurements for subjects 20 and 21 in study GS-US-104-0312 is not assured. The data for subjects 20 and 21 in study GS-US-104-0312 should be excluded from bioequivalence assessments.

Data from the analytical portions of study GS-US-104-0312 (except subjects 20 and 21) and of study GS-US-104-0352 can be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.
Bioequivalence Branch, DBGC

Final Classifications:

NAI (Clin) - Comprehensive Clinical Development, Tacoma, WA
FEI 3002998793

VAI (Clin) - Hospital del Niño Infectology Service, Panama City,
PANAMA
FEI 3004435925

VAI (Anal) - Gilead Sciences, Foster City, CA
FEI 1000523075

cc:

OSI/Ball

OSI/DBGC/Moreno/Salewski/Dejernet/Matthews

OSI/DBGC/BB/Haidar/Skelly/Dasgupta/

OTS/OCP/DCPIV/Lazor/Green/Robertson

OND/OAP/DAVP/Birnkrant/Katherine Schumann

PA-FO/SEA-DO/SIB/Tait

CE-FO/BLT-DO/INV/MGN-WV/Bretz

PA-FO/SAN-DO/SFIB/Foley

Draft: AD 12/16/11

Edit: MFS 12/19/11

OSI: File BE6247

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/s/

ARINDAM DASGUPTA

12/19/2011

Edits done

MICHAEL F SKELLY

12/19/2011

Skelly signing on behalf of Dr. Haidar

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 14, 2011

To: Debra Birnkrant, MD, Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name), dosage form, Application Number VIREAD (tenofovir disoproxil fumarate) oral powder, NDA 22-577
VIREAD (tenofovir disoproxil fumarate) tablets, NDA 21-356/S-038

Applicant: Gilead Sciences, Inc.

OSE RCM #: 2011-2407

1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for VIREAD (tenofovir disoproxil fumarate) oral powder.

The purpose of the Applicant's submission is to seek approval of original New Drug Application (NDA) 22-577 proposing a pediatric oral formulation of VIREAD (tenofovir disoproxil fumarate), in response to an FDA Pediatric Written Request.

The Applicant also submitted a simultaneous CMC supplement (S-038) on June 16, 2011 to approved NDA 21-356. This supplement proposes reduced strength tablets (150-, 200-, and 250- mg strengths) for pediatric patients who weigh 17 to less than 35 kg and are able to swallow tablets. DAVP is reviewing this supplement in conjunction with the first cycle review for NDA 21-356.

2 MATERIAL REVIEWED

- Draft VIREAD (tenofovir disoproxil fumarate) oral powder and tablets Patient Package Insert (PPI) received on June 16, 2011 and further revised by the Applicant to include Instructions for Use on October 13, 2011; revised by the Review Division and provided to DMPP on December 5, 2011.
- Draft VIREAD (tenofovir disoproxil fumarate) oral powder and tablets Prescribing Information (PI) received June 16, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on December 5, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- focused on the proposed revisions to the PPI (including the added IFU) related to PI revisions for NDA 22-577 and sNDA21-356/038
- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- The enclosed IFU review comments are collaborative DMPP and DMEPA comments.

4 DISCUSSION

Based on recommendations from DRISK and DMEPA, DAVP sent the Applicant a Request for Information letter on October 4, 2011. The letter requested that the Applicant submit Instructions for Use (IFU) to be included at the end of the PPI to provide detailed instructions for patients/caregivers regarding the measurement of one half scoop and one full scoop of the oral powder. Additionally, the letter provided the suggestion that the Applicant may wish to perform a simulated use study or label comprehension study with representative users to validate that the IFU are adequate.

DRISK performed a comprehensive review on July 28, 2011 to bring the PPI up to current patient labeling standards. This review focuses on revisions to the PPI (including the added IFU section) related to revisions to the PI for NDA 22-577 and sNDA 21-356/038.

5 CONCLUSIONS

The PPI is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
12/14/2011

BARBARA A FULLER
12/14/2011

LASHAWN M GRIFFITHS
12/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 9, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) & Strength(s): Viread (Tenofovir Disoproxil Fumarate) Tablets
150 mg, 200 mg, 250 mg
Viread (Tenofovir Disoproxil Fumarate) Oral Powder
40 mg per scoop

Application Type/Number(s): NDA 021356/S-038
NDA 022577

Applicant/sponsor: Gilead

OSE RCM #: 2011-2669 and 2011-2403

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed carton labeling and container labels for Viread (Tenofovir Disoproxil Fumarate) Tablets, 150 mg, 200 mg, and 250 mg and Viread Oral Powder, 40 mg per scoop, for areas of vulnerability that can lead to medication errors in response to a request by the Division of Anti-Viral Products (DAVP).

1.1 REGULATORY HISTORY

Viread 300 mg tablets, was approved on October 26, 2001 and is used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 18, 2011 and the October 13, 2011 submission:

Tablets:

- Established Name: tenofovir disoproxil fumarate
- Indication of Use: use in combination with other antiretroviral agents for the treatment of HIV-1 infections in pediatric patients 2 years of age but less than 18 years of age
- Route of administration: Oral
- Dosage form: Tablets
- Dose: One tablet by mouth daily with or without food
- How supplied:
 - 150 mg tablets are triangle-shaped white film-coated, debossed with “GILEAD” on one side and “150” on the other side
 - 200 mg tablets are round-shaped, white, film-coated, debossed with “GILEAD” on one side and “200” on the other side
 - 250 mg tablets are capsule-shaped, white, film coated, debossed with “GILEAD” on one side and “250” on the other side
- Storage: 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure systems: 30 count bottles with child-resistant closures

Oral Powder:

- Established Name: tenofovir disoproxil fumarate
- Indication of Use: use in combination with other antiretroviral agents for the treatment of HIV-1 infections in pediatric patients 2 years of age and adults unable to swallow the tablets
- Route of administration: Oral
- Dosage form: Oral Powder

- Dose: Pediatric Patients: 8 mg/kg once daily with food. Adults: 300 mg of the oral powder (7.5 scoops)
- How supplied: multi-use bottle co-packaged with a dosing scoop
- Storage: 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure systems: 250 mL HDPE bottle with induction seal and child-resistant closure

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Tablet Container Labels submitted June 16, 2011
- Oral Powder Container Labels submitted October 12, 2011
- Oral Powder Carton Labeling submitted October 12, 2011
- Instructions for Use submitted November 3, 2011

Additionally, since Viread is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Viread. On November 2, 2011 an AERS search was conducted using the following search terms: trade name “Viread”, and verbatim term “Virea%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” and the High Level Term (HLT) “Product Label Issues”. No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (e.g. adverse events) and intentional overdoses.

Following exclusions there were no cases relevant to this review.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following section describes the deficiencies identified in our assessment of the labels and labeling.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 CONTAINER LABELS FOR THE ORAL POWDER AND PRESCRIBING INFORMATION

- A statement should be included that reads “Viread Powder should not be administered via nasogastric or any other feeding tubes.”

This recommendation was discussed during the November 29, 2011 labeling meeting. The review division did not agree that this statement is necessary on the labels because: (1) it is physically impossible to administer soft foods such a yogurt through a nasogastric tube and (2) the label indicates that the powder should be mixed with soft foods and not with liquids. It was agreed at the meeting to bold the statement that indicates that the powder should not be mixed with liquids.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors. We recommend the following:

A. All Labels and Labeling

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
2. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXXX-x). Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.
3. Revise the dosage statement [REDACTED] (b) (4) [REDACTED] to read “Usual Dosage: See Prescribing Information”

B. Container Label for Tablets (150 mg, 200 mg, 250 mg)

1. Revise the grey color blocking scheme used to highlight the strength statement on the labels to use a distinct color for each strength that provides adequate differentiation. The current color blocking scheme uses the same grey color for all three strengths and does not provide adequate visual differentiation.
2. Relocate the strength statement to immediately follow the dosage form statement as presented below.

Viread
(Tenofovir Disproxil Fumarate) Tablets
XXX mg

3. Relocate the net quantity statement (i.e. 30 tablets) to the bottom of the label, away from the strength statement.
4. Delete the graphic image of the tablet on the principal display panel or replace it with an image of the actual Viread tablet.

C. Container Label & Carton Labeling for Oral Powder

1. Revise the strength statement from (b) (4) to read “40 mg/scoop”.
2. Relocate the net quantity statement (i.e. 60 grams per bottle) to the bottom of the label, away from the strength statement.
3. Under the Usual Dosage statement, include the following:
Viread oral powder should only be mixed with soft foods. Do not mix with liquids.

D. Instructions for Use

DMEPA’s recommendations on the Instructions for Use section of the PI were discussed with the Patient Labeling Reviewer and included in their review. We recommended:

- All figures should be placed adjacent to the appropriate text and labeled sequentially such as Figure A, Figure B, etc. Reference each figure in the text as for example, “See Figure A”
- Add under Important Information “Give the entire dose right away after mixing to avoid a bad taste”

If you have further questions or need clarifications, please contact Brantley Dorch, project manager, at 301-796-0150.

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/s/

CARLOS M MENA-GRILLASCA on behalf of LISSA C OWENS
12/09/2011

CARLOS M MENA-GRILLASCA
12/09/2011

CAROL A HOLQUIST
12/12/2011

Clinical Consultation
DRUP Track Correspondence No. 264

FROM: Stephen Voss MD, Medical Officer DRUP

THROUGH: Theresa Kehoe MD, Medical Team Leader DRUP
Audrey Gassman MD, Acting Deputy Division Director DRUP

TO: Division of Antiviral Products:
Katherine Schumann MS, Regulatory Project Manager
Tafadzwa Vargas-Kasambira MD, MPH, Clinical Reviewer
Linda Lewis MD, Clinical Team Leader

SUBJECT: **Viread® (tenofovir disoproxil fumarate) pediatric bone toxicity data and new pediatric dosage form, NDA 022577 (Gilead Sciences)**

DATE CONSULT RECEIVED: August 11, 2011

DATE CONSULT COMPLETED: November 18, 2011

Administrative background

Viread (tenofovir disoproxil fumarate = TDF) is a pro-drug of tenofovir, a nucleotide analog reverse transcriptase inhibitor (NRTI). Viread 300 mg tablet once daily is currently approved (NDA 021356) as part of combination treatment for HIV infection in adult and adolescent patients (≥ 12 y/o and weighing ≥ 35 kg), and for treatment of chronic hepatitis B in adults. Viread has shown the potential to adversely affect bone metabolism in animal and human studies. DMEP and DRUP have previously provided consultation on bone-related data from studies in HIV-infected adults (review in DARRTS 04-Apr-2005) and adolescents (review in DARRTS 10-Feb-2010). These data are described in labeled Warning & Precaution Section 5.6 Decreases in Bone Mineral Density.

For the treatment of younger children, the Applicant has developed a new oral powder formulation (40 mg TDF/1 g powder). A phase 3 trial, GS-US-104-0352, is being conducted in HIV-infected children (age 2 - < 12, weighing 10 kg to 35 kg) using the powder at a dose of ~ 8 mg/kg to a maximum 300 mg, which was intended to provide systemic exposure comparable to that in adults and adolescents. (At maximal dose, the marketed 300 mg tab was allowed as an alternative.) Following the initial 48-week randomized treatment period of this trial, the Applicant also developed reduced-strength tablets (150 mg, 200 mg, 250 mg) as a proposed alternative to the powder for older children, i.e. age ~ 6 -11 y/o. They now submit concurrently a new NDA (**022577**) for the powder formulation, which includes the new clinical data; and an sNDA (**021356/S-038**) for the reduced-strength tablets. DRUP is asked to provide assistance with review of the bone metabolism data (bone mineral density and biochemical markers), and advice regarding update of the bone-related labeling for the pediatric population. The PDUFA goal date is 18-Jan-2012 (priority review).

HIV and TDF effects on bone metabolism

HIV infection has been associated with reduced bone mineral density (BMD) in adults and children, compared to uninfected individuals. The mechanism of bone loss, and the clinical significance (i.e. effect on fracture risk), are unknown. Increasingly, antiviral treatment also appears to contribute to bone loss: several different regimens have been associated with BMD reductions over the first 6-12 months of treatment, generally followed by stabilization after 1-2 years or slight improvement. Such BMD reductions, in several studies, appear to be greater with regimens that include tenofovir.

Animal studies: Tenofovir (TDF) treatment resulted in bone toxicity manifested as reduced BMD and increased bone turnover markers in young-adult rats and dogs. These effects were seen at 30 mg/kg/day in dogs with a NOAEL for bone effects of 10 mg/kg/day. Infant SIV-infected rhesus monkeys treated for short periods (up to 12 weeks) with TDF 4-30 mg/kg/day showed normal health and growth, and normal BMD. However, 30 mg/kg/day for longer periods (>8-21 months) led to toxicity in all animals including proximal renal tubule dysfunction with increased urinary phosphorus and decreased serum phosphorus; decreased TDF clearance; increased alkaline phosphatase; and various bone lesions/deformities including widened growth plates, growth restriction, osteopenia, osteomalacia and fractures. Reduction of the dose to 10 mg/kg/day resolved the bone abnormalities and biochemical changes.

Phase 3 trial in adults (GS-99-903): This pivotal 3-year trial of TDF in HIV-infected adults demonstrated adverse effects on BMD. This was a randomized, double-blind, multicenter study in 600 antiretroviral-naïve patients (viral load >5000 copies/mL) age 18-65 y/o (mean 35 y/o, 74% men, 64% white, 63% asymptomatic, baseline spine and hip T-scores ~ -0.3 and -0.1). Patients were divided evenly between 2 treatment groups: TDF 300 mg daily in combination with efavirenz (EFV) and lamivudine (3Tc); *versus* an active-control regimen of stavudine (d4T) also in combination with EFV and 3Tc. At week 144, there were greater declines from baseline with TDF, compared to active control, in lumbar spine BMD (-2.2% ± 3.9 vs. -1.0% ± 4.6, $p < 0.001$) and in femoral neck BMD (-2.8% ± 3.5 vs. -2.4% ± 4.5, $p = 0.064$). The bone losses occurred in the first 24-48 weeks, then stabilized with little additional change through week 144. With regard to the number of patients who experienced pronounced bone loss, 28% of tenofovir patients vs. 21% of active-control patients had a ≥ 5% decline in spine BMD and/or a ≥ 7% decline in femoral neck BMD. Bone turnover markers reflecting both bone formation and resorption, and levels of serum PTH and 1,25-OH-vitamin D, were all higher in the TDF vs. the control group. There were no differences in clinical fractures, which the study was not powered to evaluate.

An **open-label extension** of this trial was conducted as a PMC: 86 subjects from the TDF arm and 85 subjects from the control arm received TDF, EFV and 3Tc for 4 additional years. At DAVP request, all subjects also received calcium and vitamin D supplements, which had not been given in the double blind phase. Subjects transitioning from the double blind TDF arm had essentially no further change in spine or hip BMD over 4 years in the open label phase. Subjects transitioning from the d4T (control) arm to TDF had, against expectation, a small increase of ~1% in spine BMD at 2.5-3.5 years of OL phase, then returned to OL baseline. In contrast, hip BMD for this group declined by ~1.5-2% in the first OL year, followed by stabilization at this level for the remainder of the 4 years. Thus compared to the TDF group during the double blind

phase, this control→TDF group appeared to have less bone loss. DAVP reviewers concluded that this may have been related to the calcium/vitamin D supplements given to the latter group. However, other factors could not be ruled out due to the study's design.

Postmarketing reports of a Fanconi like syndrome associated with TDF treatment began to appear several years ago. Fanconi's is a manifestation of a defect in proximal renal tubular reabsorption of multiple substances including phosphate, and if untreated it may result in osteomalacia. Some of the TDF cases manifested with bone pain and had bone scans consistent with osteomalacia and fractures, though bone biopsies were not done so the diagnosis of osteomalacia is uncertain. Symptoms usually resolved after stopping TDF. Some proposed cofactors for this toxicity include dose relative to body size and concomitant treatments including ritonavir and NSAIDs. Most of these reports have involved adult patients; there have also been 4 spontaneous reports of pediatric (age 10-16) bone events (diagnosed as rickets by X-ray criteria) associated with proximal renal tubulopathy with hypophosphatemia.

Pediatric trials of TDF: Unlike adults, who typically experience gradual BMD decline of ~0.5% to 1%/year, healthy children and adolescents experience rapid, progressive increases in BMD. This is in part because of a true increase in density per unit of bone volume, and in part because the 2-dimensional "areal" DXA technique does not correct for bone depth, therefore will tend to "overestimate" BMD as bones enlarge. Contrary to the expected increases, a preliminary, uncontrolled pediatric study (GS-01-926) of TDF in 18 HIV-infected patients age 6-16 y/o showed an absolute decline (-2.0%) in mean lumbar spine BMD in the first year of TDF treatment, despite normal bone growth. Another prospective pediatric TDF study¹ also showed absolute BMD declines in 5 of 6 patients, including declines of 10% and 27% in two patients; however a third study² involving 16 children and adolescents showed no adverse effect on BMD accrual.

Adolescent trial (GS-US-104-0321): This phase 3 controlled trial, conducted in response to a Pediatric Written Request and reviewed in 2009-2010, involved 87 HIV-infected adolescents (age 12-17 inclusive, 56% female, 100% Hispanic, weighing >35 kg) who were failing their current drug regimen. Subjects were initially stabilized on an optimized background regimen (OBR) of 3-5 other antiretroviral agents, and then randomized to add either TDF 300 mg daily or placebo to this regimen. After 48 weeks (or sooner if on placebo and failing to meet an efficacy endpoint), completers could then receive TDF in an open label extension phase.

At baseline, because of their disease, subjects were behind their peers in growth and bone density, with Z-scores (adjusted for age/gender) of approx. -1 for height, weight and lumbar spine BMD (i.e. ~1 SD below mean). During the initial 48-week (double-blind) phase of the study, mean lumbar spine and total body BMD increased significantly from baseline in both treatment groups, though somewhat less than expected for a healthy adolescent population (**Table 1**). Increases were somewhat lower in the TDF group relative to placebo for lumbar spine BMD; this difference was not significant, however the trial very likely lacked statistical power for this comparison. There were 6 TDF subjects, vs. 1 placebo subject, who experienced a potentially clinically significant (> 4%) loss in lumbar spine BMD at 48 weeks. After 96 weeks of TDF treatment, 25% of subjects were below their baseline lumbar spine BMD, and 25% were below their baseline total body BMD.

Table 1. Study GS-US-104-0321 (adolescents): Bone Mineral Density, mean percent change (SD) from baseline by treatment group (RAT)

	TDF + OBR	Placebo + OBR	All TDF cohort
% Change in Lumbar Spine BMD			
Week 24	1.20 (4.96)	1.93 (4.52)	1.32 (4.73)
Week 48	3.15 (7.29)	3.81 (4.98)	3.06 (6.23)
Week 96	-	-	7.67 (9.74)
% Change in Total Body BMD			
Week 24	0.50 (2.24)	0.83 (2.70)	0.59 (2.09)
Week 48	1.50 (3.11)	1.52 (3.81)	1.46 (3.08)
Week 96	-	-	3.34 (5.21)
Note: expected rates of increase in adolescents' BMD are ~5-10%/year (lumbar spine) and ~3-6%/year (total body) (Ref. 3, 4)			

Bone density mean Z-scores declined modestly from their low baseline, reflecting that the subjects' BMD accrual continued to lag behind their peer groups', though the changes from baseline were not statistically significant. (Table 2) The declines were slightly greater in the TDF group than in the placebo group; this difference was also not statistically significant. Because body height Z-scores increased slightly in the TDF group over the same time period, and dropped slightly in the placebo group, the BMD trends cannot be explained by impairment of bone growth.

Table 2. Study GS-US-104-0321 (adolescents): Bone Density Z-scores, mean change (SD) from baseline by treatment group (RAT)

	TDF + OBR	Placebo + OBR	All TDF*
Change in Lumbar Spine Z-score			
Week 24	-0.17 (0.49)	-0.12 (0.32)	-0.15 (0.45)
Week 48	-0.22 (0.62)	-0.17 (0.37)	-0.24 (0.51)
Week 96	-	-	-0.34 (0.60)
Change in Total Body Z-score			
Week 24	-0.18 (0.35)	-0.12 (0.21)	-0.17 (0.32)
Week 48	-0.25 (0.39)	-0.18 (0.35)	-0.25 (0.42)
Week 96	-	-	-0.46 (0.55)

DRUP reviewers' conclusions from these adolescent bone density data were:

- Baseline bone density was below that of the subjects' age- and gender-matched peers, due to HIV infection, co-morbidities, prior therapies and/or delayed growth
- Over 96 weeks of TDF therapy, subjects' mean lumbar spine and total body BMD increased, though probably less than expected for their peer group, and 25% were below baseline at week 96, which would be highly unusual for a healthy adolescent
- Compared to placebo, the TDF group had somewhat lesser gains in BMD at week 48; this was thought to be consistent with previous findings in adults, where the TDF group had greater declines in BMD than the active-control group; lack of statistical significance in adolescents (unlike the adults) could be attributed to much smaller scale and duration of study
- Linear bone growth in the TDF group was overall unaffected

Also consistent with the adult study, the adolescent TDF cohort showed increases in the circulating bone turnover markers of osteocalcin, BSAP, CTX and NTX of 21%, 5%, 31% and 14%, respectively, at week 48, and lesser changes with placebo. PTH levels increased 13% over baseline at week 48 with TDF, also similar to adults; PTH declined slightly with placebo. Serum calcium and magnesium did not change markedly. Serum phosphorus declined modestly in the first year and more so in the second year: at week 96, mean phosphorus levels were 12% below baseline. Post hoc analysis showed that All-TDF subjects who had any serum phosphorus level <3.5 mg/dL had lesser gains in BMD, height and weight over 96 weeks, relative to subjects with no levels <3.5 mg/dL, although their PTH levels were not higher. It was unclear whether the lower phosphorus levels may have directly affected bone density (e.g. by impairing mineralization), or whether both were due to other factors related to disease, nutrition, etc. There were 2 fractures in this study, both on TDF and both trauma-related.

The overall conclusion from these bone data was that TDF appeared to affect bone metabolism similarly in adults and adolescents, with a tendency to increase bone turnover and, perhaps as a result, a negative effect on BMD. The clinical significance (i.e. effect on fracture risk) was uncertain. There was no indication of any effect on bone growth. It was concluded that calcium and vitamin D supplementation and periodic BMD monitoring should be considered in any patient on long term TDF therapy, particularly in the presence of other risk factors for bone loss or fracture. Current labeling section 5.6 Decreases in Bone Mineral Density includes a summary of these findings and recommendations, and also indicates the apparent risk of osteomalacia related to renal tubule defects.

None of the aforementioned protocols included measurement of urinary parameters such as phosphate. In order to help delineate the mechanism of TDF's skeletal effects, and their relationship if any to proximal renal tubule dysfunction, approval of Viread to treat HIV-infected adolescents in March 2010 included a PMR evaluating the following in pediatric subjects:

- Serum and urine calcium, phosphate, magnesium, bicarbonate, with calculation of renal phosphate threshold (T_{mp}/GFR)
- Bone turnover markers: osteocalcin, BSALP, CTX, NTX, PTH, 25-OH-vitamin D, 1,25-OH-vitamin D
- Correlation of renal parameters with BMD

These assessments have been incorporated into protocol GS-US-174-0144 involving HBV-infected children (submitted July 2011, #0647).

Current submission: HIV-infected children age 2 to < 12 y/o

The Applicant is seeking a new Viread indication for this younger population and has submitted reports of two new clinical studies:

- **GS-US-104-0312**, a PK crossover study comparing 300 mg of the new oral powder with the marketed 300 mg tablet, in 32 healthy adult volunteers. This study did establish bioequivalence by AUC criteria, but C_{max} of the powder was 27% lower than the tablet. The latter was attributed by the Applicant to coating of the granules, which is used to mask the unpalatability of the drug. They did not consider the difference in C_{max} to be clinically significant because of the equivalence of AUC and the long intracellular half-life (≥ 60 hrs) of tenofovir.

- **GS-US-104-0352**, a Pediatric Written Request phase 3 efficacy/safety study in children using the new oral powder (see below). This study also included a PK substudy in 23 subjects who had received at least 4 weeks of TDF (8 mg/kg) treatment: compared to historical PK data with 300 mg in adults, the powder resulted in C_{max} that was ~19-32% lower and AUC that was ~6-22% lower.

Trial GS-US-104-0352: A Phase 3, 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

This ongoing ~5 year (240 weeks) study is being conducted at 1 site in Panama (n=72 subjects), 6 sites in the US (n=22) and 2 sites in the UK (n=3). The study population consists of HIV-1 infected children (age 2-11 inclusive) with HIV controlled (low viral load, high CD4 count) on a stable HAART regimen containing one of the NRTIs **stavudine (d4T)** or **zidovudine (ZDV)** at entry. The objective is to investigate the long-term efficacy, safety and tolerability of substituting **tenofovir (TDF)** for the active-control d4T or ZDV within the antiretroviral regimen. The efficacy endpoints (at week 48) are defined by non-inferiority in HIV-1 RNA levels and CD4 cell counts. Safety endpoints include BMD, bone turnover markers, PTH, vitamin D, and calcium/ phosphorus serum levels.

Study Design:

During the initial 48-week phase, subjects were randomized 1:1 to continue (open-label) treatment with d4T or ZDV, or to switch to TDF oral powder 8 mg/kg daily (in applesauce or similar soft food, up to maximum 300 mg). Subjects weighing > 37 kg had the option to use the marketed TDF (Viread) 300 mg tablet as an alternative to 300 mg of the powder. In both treatment groups, the other elements of each subject's pre-existing HAART regimen were continued. No substitution of d4T, ZDV or TDF was allowed during the first 48 weeks. All subjects who completed 48 weeks then had the option to receive open-label TDF (still continuing the rest of their HAART regimen) during each of two consecutive 96-week extension periods. Analyses beyond 48 weeks were based on an "All TDF" cohort consisting of data from the time of each subject's initiation of TDF (i.e. either study week 0 or 48). The NDA 022577 contains both 48-week and 96-week interim study reports.

Population:

Inclusion criteria:

- HIV-1 infected male or female children (age 2-11 inclusive, or 2-15 y/o for several subjects rolling over from Study GS-US-162-0111)
- Plasma HIV-1 RNA levels <400 copies/mL (considered to represent "virologic suppression")
- Receiving combination antiretroviral therapy which included either stavudine (d4T) or zidovudine (ZDV) for at least 12 weeks
- Naïve to TDF
- AST and ALT $\leq 3x$ ULN
- Adequate hematologic function

- Adequate renal function: serum creatinine ≤ 0.8 mg/dL for age 2-4 y/o, ≤ 1.0 mg/dL for age 5-9 y/o, or ≤ 1.2 mg/dL for age 10-15 y/o; calculated creatinine clearance ≥ 80 mL/min/1.73m²
- Serum amylase $< 1.5x$ ULN (or if $\geq 1.5x$ ULN, serum lipase $\leq 1.5x$ ULN)
- Negative pregnancy test (postmenarchal females)
- Willing to use 2 forms of contraception (sexually active males and females)
- Parental consent

Exclusion criteria (relevant to bone toxicity):

- Need for ongoing therapy with any of the following (OK if discontinued for ≥ 30 days at entry and throughout study):
 - Nephrotoxic agents (as listed in protocol)
 - Systemic chemotherapy
 - Systemic corticosteroids (short courses < 2 wks allowed)
 - Interleukin-2 or other immunomodulating drugs
 - Investigational agents (except with Gilead approval)
- Evidence of a GI malabsorption syndrome or chronic nausea or vomiting which may confer an inability to receive p.o. medication
- History of significant renal disease
- History of significant bone disease (i.e. osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochondroses, multiple bone fractures)

There were no exclusion criteria related to calcium, vitamin D or PTH levels, and no calcium or vitamin D supplements were required. The protocol specified that subjects with a confirmed Grade 3 or 4 hypophosphatemia were to be given phosphate supplementation of 20 mg/kg/day; they were then to have levels repeated every 2 weeks until Grade 1 or less at which time the supplements could be discontinued.

Results

Disposition:

Of 97 randomized and treated (at least one dose, “RAT”) subjects, 92 completed the 48-week randomized treatment period. None of the 5 dropouts in this period were due to an AE, and there were no deaths.

Of the 48 subjects assigned to TDF, 44 completed the initial 48 weeks; 38 of these then entered the open label TDF phase (week 48 \rightarrow 240). Of the 49 subjects assigned to d4T/ZDV, 48 completed the initial 48 weeks, and 41 of these entered the open label TDF phase. At the time of the week 96 interim analysis, 71 of the 79 subjects who had entered the OL phase remained ongoing in the study. Of the 8 who discontinued during the OL phase, 4 were related to AEs: 3 subjects with hypophosphatemia (9004, 9030 and 9071) and 1 with glycosuria (9046) (see below).

The All TDF group for analysis consisted of 89 subjects: all 48 subjects assigned to TDF in the 48 week randomized phase, and the 41 subjects initially assigned to d4T/ZDV who enrolled in the OL phase.

Demographics

Of the 97 subjects, 72 (74%) were at a single site in Panama. Most were considered Mestizo (mixed European/native American ancestry, 67% of subjects) and Hispanic/Latino (79%). About half were male and average age was 7 y/o (Table 3). All subjects were within the protocol's originally specified age at entry of 2-11 y/o, except for 5 subjects rolling over from Study GS-US-162-0111): 2 of these were age 12 and 1 each were age 13, 14, and 15 at entry. Most subjects were below reference means for height and weight, reflecting some delayed growth despite their good level of HIV viral suppression.

Table 3. Study GS-US-104-0352: Demographics and baseline characteristics by treatment group (RAT)

	TDF N = 48 n (%)	d4T or ZDV N = 49 n (%)	Total N = 97 n (%)
Gender			
Male	21 (44)	29 (59)	50 (52)
Female	27 (56)	20 (41)	47 (48)
Age (years)			
Mean (SD)	7 (3.3)	7 (2.6)	7 (3.0)
Race			
American Indian/Alaska Native	2 (4)	0	2 (2)
Asian	1 (2)	0	1 (1)
Black	13 (27)	6 (12)	19 (20)
Mestizo	28 (58)	37 (76)	65 (67)
White	3 (6)	6 (12)	9 (9)
Other	1 (2)	0	1 (1)
Ethnicity			
Hispanic	35 (73)	42 (86)	76 (85)
Non-Hispanic	13 (27)	7 (14)	13 (14)
Weight (kg)			
Mean (SD)	26 (12)	24 (7.7)	25 (10.1)
Range	10.1 – 63.3	10.2 – 45	10.1 – 63.3
Z-score (Mean)	-0.46	-0.49	-0.48
Height (cm)			
Mean (SD)	118 (19.8)	119 (16.7)	119 (18.2)
Range	78 – 155	82 – 152	78 - 155
Z-score (mean)	-1.08	-0.94	-1.01

Concomitant medications

One subject, who had substantial bone loss, used multiple neuropsychiatric medications of sertraline, risperidone, divalproex, methylphenidate and dexmethylphenidate, which preceded the study and were continued through the study. Otherwise, there did not appear to be use of any concomitant medications that would interfere with bone density data. Several subjects used oral prednisone but none for more than 8 days consecutively.

Bone Mineral Density

DXA scans of lumbar spine and total body (including head) were performed at baseline and at 24-week intervals throughout both randomized and extension phases. Scans were centrally read at (b) (4) which used an unspecified reference database to assign BMD Z-scores based on each subject's age, gender and race. (The DXA Procedural Manual was not included in the NDA.) However, reference data are very sparse for younger children, and (b) (4) had none available for children who were 5 y/o or younger. Therefore consultation was provided by (b) (4) who (blinded to treatment assignment) supplied BMD Z-scores and interpretation for subjects who were < 5 y/o at baseline. (b) (4) also provided independent analysis and interpretation of all data related to BMD, BMD Z-scores and bone turnover markers.

Lumbar Spine BMD

At baseline, the TDF group had somewhat lower L1-L4 BMD and Z-scores than the d4T/ZDV (control) group. (Table 4) During the initial, randomized 48-week phase, this TDF group experienced BMD increases that were slightly less than the control group. At week 48 (randomized phase), 5/42 TDF subjects were below baseline BMD vs. 1/44 control subjects, and 1 TDF subject was >4% below baseline BMD vs. no control subjects. Spine BMD increases of ~5%/year continued in the subsequent 2 years of open-label TDF treatment, which is consistent with reference rates in healthy children.

Reviewer comment: In the previous adolescent study (GS-US-104-0321), 25% of All-TDF subjects were below their baseline lumbar spine BMD at week 96. In the new study, only 8% were below baseline at week 96, and only 4% (1 subject out of 25) at week 144. The latter was one of 3 subjects in the trial who had probable proximal renal tubule dysfunction with significant hypophosphatemia (see below), and whose BMD remained 13.79% below baseline.

Out of 89 subjects who received TDF, there were 13 who had lumbar spine BMD more than 4% below baseline at one or more subsequent timepoints. These 13 subjects, together with 3 others who met this criteria for total body BMD, had baseline BMD Z-scores that were lower than the other 73 subjects (median -1.115 vs. -0.753). At their last available BMD measurement, 7 of the 13 subjects were above their baseline and 6 were below (-13.79%, -7.37%, -5.04%, -4.27%, -3.31% and -0.29%).

Table 4. Study GS-US-104-0352: L1-L4 Spine BMD – Percent Change from baseline by treatment group (RAT)

	TDF (randomized phase) (N = 48)	d4T or ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Baseline (BL)			
N	46	46	87
BMD, Mean (SD) (g/cm ²)	0.604 (0.12)	0.621 (0.10)	0.626 (0.12)
p-value: TDF vs. d4T/ZDV*	0.36		
Z-score, Mean (SD)	-1.034 (1.01)	-0.498 (1.04)	

Week 24			
N	43	46	83
Mean % change from BL(SD)	2.718 (3.95)	3.300 (3.31)	1.992 (4.01)
Range	-4.64, 13.37	-3.32, 9.31	-7.47, 13.37
p-value: TDF vs. d4T/ZDV *	0.25		
# with increased BMD	30	37	54
# with decreased BMD	13	8	29
# with > 4% decrease in BMD	1	0	5
Week 48			
N	42	44	83
Mean % change from BL (SD)	4.696 (4.63)	5.105 (3.00)	4.174 (5.34)
Range	-7.37, 16.82	-0.43, 11.31	-7.37, 20.99
p-value: TDF vs. d4T/ZDV *	0.69		
# with increased BMD	37	43	65
# with decreased BMD	5	1	16
# with > 4% decrease in BMD	1	0	4
Week 72			
N			72
Mean % change from BL (SD)			5.901 (7.48)
Range			-12.27, 27.37
# with increased BMD			58
# with decreased BMD			14
# with > 4% decrease in BMD			2
Week 96			
N			64
Mean % change from BL (SD)			9.598 (8.93)
Range			-15.00, 33.63
# with increased BMD			59
# with decreased BMD			5
# with > 4% decrease in BMD			3
Week 120			
N			30
Mean % change from BL (SD)			13.556 (9.54)
Range			(-15.61, 38.59)
# with increased BMD			28
# with decreased BMD			2
# with > 4% decrease in BMD			2
Week 144			
N			25
Mean % change from BL (SD)			17.113 (10.87)
Range			(-13.79, 40.84)
# with increased BMD			24
# with decreased BMD			1
# with > 4% decrease in BMD			1
* p-value from Wilcoxon rank sum test			
Source: Table 43.1 of both Week-48 and Week-96 Study Reports, ADDEXA week 96 dataset			

Within the control group in the randomized phase, 30 subjects were continuing pre-study treatment that included ZDV, and 18 subjects were continuing d4T. There were no apparent differences between these 2 subgroups with respect to lumbar spine BMD. (Table 5)

Table 5. Study GS-US-104-0352: L1-L4 Spine BMD – Percent Change from baseline by treatment group and subgroups of control group (RAT)

	TDF (randomized phase) (N = 48)	ZDV (randomized phase) (N = 30)	d4T (randomized phase) (N = 18)
Baseline (BL)			
N	46	29	17
BMD, Mean (SD) (g/cm ²)	0.604 (0.12)	0.622 (0.09)	0.619 (0.12)
Week 24			
N	43	29	17
Mean % change from BL(SD)	2.718 (3.95)	3.625 (3.10)	2.746 (3.66)
Range	-4.64, 13.37	-3.32, 9.31	-2.70, 9.19
p-value: ZDV vs. d4T *		0.24	
# with increased BMD	30	25	12
# with decreased BMD	13	4	4
# with > 4% decrease in BMD	1	0	0
Week 48			
N	42	27	17
Mean % change from BL(SD)	4.696 (4.63)	4.697 (2.51)	5.752 (3.64)
Range	-7.37, 16.82	-0.43, 8.06	0.19, 11.31
p-value: ZDV vs. d4T *		0.53	
# with increased BMD	37	26	17
# with decreased BMD	5	1	0
# with > 4% decrease in BMD	1	0	0
* p-value from Wilcoxon rank sum test (JMP)			
Source: ADDEXA dataset			

Lumbar spine Z-scores (i.e. BMD normalized for age, gender and race) confirm that the overall study population (age 2-11 y/o) experienced essentially normal accrual of lumbar spine BMD during the study, with no evidence of any deleterious effect of TDF treatment. (Table 6) Baseline Z-scores were moderately low, particularly in the treatment group randomized to TDF. Over the 48 week randomized phase, there were slight increases from baseline spine Z-score in both treatment groups, which were slightly greater in the control group. In the extension phase, there continued to be essentially no change from baseline over a total of 3 years. From baseline to week 96, shifts in Z-score category (>-1.0, -1.0 to -2.5, <-2.5) occurred in 13/64 subjects with improvement in 7 and worsening in 6.

Reviewer comment: These data showing no apparent adverse effect of TDF on lumbar spine BMD, either in the randomized phase (relative to control group) or over 3 years of treatment (relative to reference values), are somewhat more favorable than those from the previous adolescent study, in which lumbar spine Z-scores declined over 2 years. The newer data are also more robust than the adolescent data, as they include many more BMD measures at 2-3 year timepoints.

Table 6. Study GS-US-104-0352: L1-L4 Spine Z-score – Change from baseline by treatment group (RAT)

	TDF (randomized phase) (N = 48)	d4T/ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Baseline (BL)			
N	46	46	87
Mean (SD)	-1.034 (1.01)	-0.498 (1.04)	-0.794 (1.04)
p-value: TDF vs. d4T/ZDV *	0.028		
Week 24			
N	44	48	84
Mean Change from BL(SD)	0.081 (0.37)	0.090 (0.28)	0.017 (0.35)
Range	-0.69, 1.25	-0.51, 0.86	-3.20, 2.10
p-value: TDF vs. d4T/ZDV *	0.73		
# with increased Z-score	25	29	
# with decreased Z-score	19	17	
# with > 1 SD decrease in Z-score	0	0	
Week 48			
N	42	44	83
Mean Change from BL (SD)	0.032 (0.36)	0.087 (0.27)	0.000 (0.40)
Range	-0.54, 1.13	-0.6, 0.77	-0.83, 1.69)
p-value: TDF vs. d4T/ZDV *	0.41		
# with increased Z-score	23	27	37
# with decreased Z-score	19	17	45
# with > 1 SD decrease in Z-score	0	0	0
Week 72			
N			72
Mean Change from BL (SD)			-0.030 (0.53)
Range			-1.14, 1.85
# with increased Z-Score			30
# with decreased Z-Score			42
# with > 1 SD decrease in Z-Score			2
Week 96			
N			64
Mean Change from BL (SD)			-0.012 (0.65))
Range			-1.53, 2.16
# with increased Z-Score			26
# with decreased Z-Score			38
# with > 1 SD decrease in Z-Score			2
Week 120			
N			30
Mean Change from BL (SD)			0.028 (0.65)
Range			-1.79, 0.98
# with increased Z-Score			16
# with decreased Z-Score			14
# with > 1 SD decrease in Z-Score			2

Week 144			
N			25
Mean Change from BL (SD)			-0.033 (0.70)
Range			-1.83, 1.19
# with increased Z-Score			15
# with decreased Z-Score			10
# with > 1 SD decrease in Z-Score			2
* p-value from Wilcoxon rank sum test			
Source: Table 44.1 of both week-48 and week-96 Study Reports; ADDEXA datasets			

Lumbar Spine: Age Subgroups

When age subgroups are examined, it appears that younger children (age 2-5 y/o at entry) had more favorable results than the older group. The younger children experienced mean L1-L4 BMD increases of ~6% over the first year with no apparent difference between treatment groups. These younger children showed similar gains during the 2nd and 3rd years, with no subjects remaining below their baseline BMD. (Table 7) Improving Z-scores for this age group confirm that there was no evidence of any negative effect from TDF treatment. (Table 8)

In contrast, the older children (age 6-11 y/o at entry) had somewhat slower BMD accrual (~3-4%/year) during the first 2 years, reflected as slight declines in Z-score. Within the 1st (randomized) year, the 6-11 y/o subjects receiving TDF had significantly lower lumbar spine BMD increases compared to the control group at week 24 though not at week 48, and had more subjects with BMD declines below baseline. (During the 3rd year, the older group compared more favorably to the younger group, but numbers were much smaller.)

Table 7. Study GS-US-104-0352: L1-L4 Spine BMD – Percent Change from baseline by age group* and treatment group (RAT)

	Age 2-5 y/o		Age 6-11 y/o	
	TDF (randomized phase) (N = 16)	d4T/ZDV (randomized phase) (N = 14)	TDF (randomized phase) (N = 28)	d4T/ZDV (randomized phase) (N = 34)
Baseline (BL)				
N	14	12	28	33
BMD, Mean (SD) (g/cm ²)	0.482 (0.06)	0.535 (0.07)	0.652 (0.11)	0.645 (0.08)
Z-score, Mean	-1.293	-0.493	-0.819	-0.483
Week 24				
N	12	12	27	33
Mean % change from BL(SD)	4.680 (4.13)	3.381 (3.46)	1.499 (3.43)	3.326 (3.34)
p-value: TDF vs. d4T/ZDV **	0.50		0.018	
# with > 4% decrease in BMD	0	0	1	0
Week 48				
N	12	11	27	32
Mean % change from BL (SD)	6.245 (3.32)	5.962 (3.07)	3.457 (4.30)	4.657 (2.87)
p-value: TDF vs. d4T/ZDV **	0.82		0.33	
# with > 4% decrease in BMD	0	0	1	0

	Age 2-5 y/o All-TDF (N = 24)	Age 6-11 y/o All-TDF (N = 59)
Week 48		
N	21	57
Mean % change from BL (SD)	6.053 (5.35)	2.994 (4.86)
# with > 4% decrease in BMD	1	3
Week 72		
N	19	49
Mean % change from BL (SD)	7.835 (6.28)	4.536 (7.36)
# with > 4% decrease in BMD	1	1
Week 96		
N	17	43
Mean % change from BL (SD)	12.104 (7.47)	7.759 (8.67)
# with > 4% decrease in BMD	0	3
Week 120		
N	9	18
Mean % change from BL (SD)	12.791 (3.69)	12.061 (10.01)
# with > 4% decrease in BMD	0	2
Week 144		
N	6	16
Mean % change from BL (SD)	15.288 (4.74)	16.389 (11.73)
# with > 4% decrease in BMD	0	1
*Data not shown for 5 subjects who were age ≥12 y/o at baseline		
**p-value from Wilcoxon rank sum test (JMP)		
Source: Table 43.2, Week-48 Study Report; Table 43.3, Week-96 Study Report; ADDEXA dataset		

Table 8. Study GS-US-104-0352: L1-L4 Spine Z-score – Change from baseline by age group* and treatment group (RAT)

	Age 2-5 y/o		Age 6-11 y/o	
	TDF (randomized phase) (N = 16)	d4T/ZDV (randomized phase) (N = 14)	TDF (randomized phase) (N = 28)	d4T/ZDV (randomized phase) (N = 34)
Baseline (BL)				
N	14	12	28	33
Mean (SD)	-1.293 (0.95)	-0.493 (1.08)	-0.819 (0.99)	-0.483 (1.05)
Week 24				
N	12	12	27	34
Mean Change from BL (SD)	0.395 (0.38)	0.157 (0.32)	-0.060 (0.27)	0.062 (0.24)
Week 48				
N	12	11	27	32
Mean Change from BL (SD)	0.279 (0.37)	0.239 (0.36)	-0.094 (0.27)	0.013 (0.22)
	Age 2-5 y/o All-TDF (N = 24)		Age 6-11 y/o All-TDF (N = 59)	
Week 48				
N	21		57	
Mean Change from BL (SD)	0.263 (0.53)		-0.105 (0.29)	

	Age 2-5 y/o		Age 6-11 y/o	
	TDF (randomized phase) (N = 16)	d4T/ZDV (randomized phase) (N = 14)	TDF (randomized phase) (N = 28)	d4T/ZDV (randomized phase) (N = 34)
Week 72				
N	19		49	
Mean Change from BL (SD)	0.324 (0.56)		-0.174 (0.46)	
Week 96				
N	17		43	
Mean Change from BL (SD)	0.385 (0.73)		-0.192 (0.54)	
Week 120				
N	9		18	
Mean Change from BL (SD)	0.410 (0.35)		-0.209 (0.65)	
Week 144				
N	6		16	
Mean Change from BL (SD)	0.412 (0.46)		-0.218 (0.68)	
* Data not shown for 5 subjects who were age ≥12 y/o at baseline Source: Table 56, ISS; ADDEXA dataset				

Lumbar Spine: Gender Subgroups

There were no important differences by gender in lumbar spine BMD. Within the All TDF cohort, boys and girls alike showed minimal changes from baseline Z-score (**Table 9**)

Table 9. Study GS-US-104-0352: L1-L4 Spine Z-score – Change from baseline by gender (All TDF cohort)

	Male (N=44)	Female (N=45)
Baseline (BL)		
N	43	44
Mean	-0.832	-0.756
Week 48		
N	42	41
Mean Change from BL	0.000	-0.001
Week 96		
N	29	35
Mean Change from BL	-0.028	0.000
Week 144		
N	11	14
Mean Change from BL	-0.023	-0.035
Source: ADDEXA dataset		

Total Body BMD

Total body BMD results were notably different from those of the lumbar spine. During the 48-week randomized phase, total body BMD accrual was significantly less with TDF compared to the d4T/ZDV control group at both 24 weeks (p=0.010) and 48 weeks (p=0.043). (**Table 10**) At week 48, 9/41 TDF subjects were below baseline BMD vs. 6/45 control subjects; one subject in each group was >4% below baseline BMD.

During the open label phase, total body BMD steadily increased, though probably less than expected based on declining Z-scores (see **Table 12** below). The number of subjects who remained below baseline BMD steadily diminished; of the 25 subjects with a week 144 visit, only one had total body BMD below baseline (-18.01%). This was the same subject with persistently low lumbar spine BMD (13.79% below baseline) at week 144, who was one of 3 subjects in the trial who had probable proximal renal tubule dysfunction with significant hypophosphatemia (see below).

Out of 89 subjects who received TDF, there were 6 who had total body BMD >4% below baseline at one or more subsequent timepoints. These subjects had baseline total body BMD Z-scores that were much lower than the other 73 subjects (median -0.884 vs. -0.385). At their last available BMD measurement, 5 of these 6 subjects still had total body BMD below baseline (-18.01%, -4.41%, -4.08%, -3.85%, and -3.36%).

Table 10. Study GS-US-104-0352: Total Body BMD – Percent Change from baseline by treatment group (RAT)

	TDF (randomized phase) (N = 48)	d4T/ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Baseline (BL)			
N	47	48	88
BMD, Mean (SD) (g/cm ²)	0.798 (0.08)	0.792 (0.07)	0.802 (0.08)
p-value: TDF vs. d4T/ZDV*	0.72		
Z-score, Mean (SD)	-0.471 (1.20)	-0.386 (0.80)	
Week 24			
N	45	47	84
Mean % change from BL(SD)	0.662 (2.17)	1.492 (1.43)	0.788 (2.04)
Range	-4.80, 7.71	-1.42, 5.50	-5.292, 7.711
p-value: TDF vs. d4T/ZDV *	0.010		
# with increased BMD	39	40	57
# with decreased BMD	5	7	25
# with > 4% decrease in BMD	1	0	2
Week 48			
N	41	45	82
Mean % change from BL (SD)	1.538 (2.36)	2.603 (2.61)	1.644 (2.30)
Range	-6.32, 5.33	-4.66, 8.16	-6.316, 5.98
p-value: TDF vs. d4T/ZDV *	0.043		
# with increased BMD	32	39	64
# with decreased BMD	9	6	15
# with > 4% decrease in BMD	1	1	1
Week 72			
N			71
Mean % change from BL (SD)			2.522 (3.48)
Range			-8.77, 10.83
# with increased BMD			57
# with decreased BMD			11
# with > 4% decrease in BMD			2

	TDF (randomized phase) (N = 48)	d4T/ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Week 96			
N			64
Mean % change from BL (SD)			3.584 (4.95)
Range			-14.74, 16.79
# with increased BMD			55
# with decreased BMD			9
# with > 4% decrease in BMD			3
Week 120			
N			30
Mean % change from BL (SD)			4.522 (5.58)
Range			-14.6, 14.92
# with increased BMD			26
# with decreased BMD			4
# with > 4% decrease in BMD			1
Week 144			
N			25
Mean % change from BL (SD)			6.270 (7.70)
Range			-18.01, 20.47
# with increased BMD			23
# with decreased BMD			2
# with > 4% decrease in BMD			1
* p-value from Wilcoxon rank sum test			
Source: Table 43.3, Week 48 CSR; Table 43.4, Week 96 CSR; ADDEXA dataset			

Within the control group in the randomized phase, 30 subjects were continuing pre-study treatment that included ZDV, and 18 subjects were continuing d4T. There were no apparent differences between these 2 subgroups with respect to lumbar spine BMD. (Table 11)

Table 11. Study GS-US-104-0352: Total Body BMD – Percent Change from baseline by treatment group and subgroups of control group (RAT)

	TDF (randomized phase) (N = 48)	ZDV (randomized phase) (N = 30)	d4T (randomized phase) (N = 18)
Baseline (BL)			
N	47	30	18
BMD, Mean (SD) (g/cm ²)	0.798 (0.08)	0.795 (0.07)	0.787 (0.09)
Week 24			
N	46	29	18
Mean % change from BL(SD)	0.610 (2.18)	1.549 (1.57)	1.401 (1.21)
Range	-4.80, 7.71	-1.42, 5.50	-0.80, 4.19
p-value: ZDV vs. d4T *			0.62
# with increased BMD	28	23	16
# with decreased BMD	16	5	2
# with > 4% decrease in BMD	1	0	0

	TDF (randomized phase) (N = 48)	ZDV (randomized phase) (N = 30)	d4T (randomized phase) (N = 18)
Week 48			
N	41	27	18
Mean % change from BL(SD)	1.538 (2.36)	2.329 (2.78)	3.013 (2.36)
Range	-6.32, 5.33	-4.66, 7.25	-0.28, 8.16
p-value: ZDV vs. d4T *			0.65
# with increased BMD	31	22	16
# with decreased BMD	9	5	1
# with > 4% decrease in BMD	1	1	0
* p-value from Wilcoxon rank sum test (JMP) Source: ADDEXA dataset			

As with lumbar spine, **total body Z-score** mean was low-normal at baseline for the study population. (**Table 12**) Consistent with the total body BMD changes during the study, total body Z-scores in the randomized phase did not change in the control group but dropped somewhat in the TDF group; the difference was significant at week 48. The TDF-associated decline continued in the extension phase. After 3 years (All TDF cohort), total body Z-scores had declined by 0.454 SD, compared to decline of only 0.030 SD in lumbar spine Z-scores. In contrast, mean body height and weight Z-scores increased over 3 years by 0.34 SD and 0.08 SD, respectively.

Reviewer comment: Mean total body Z-scores appeared to decline with TDF treatment in this study to a similar degree as in the previous adolescent study, unlike lumbar spine Z-scores. Also similar to the adolescent study, growth was not impaired by TDF treatment, therefore the total body Z-score decline is likely to indicate a decline in peer-adjusted “true” i.e. volumetric bone density.

With respect to individual subjects, from baseline to week 96 in the All TDF cohort, shifts in total body Z-score category (>-1.0, -1.0 to -2.5, <-2.5) occurred in 12/64 subjects with improvement in 1 and worsening in 11 (p=0.038, Bowker test of symmetry). At weeks 96, 120 and 144, there were significant proportions of subjects who were more than 1 SD below their baseline total body BMD Z-score: 8/64, 7/30 and 6/25 subjects, respectively. There were 6 subjects who each accounted for more than one of these occurrences, 2 of whom were among the 3 subjects with probable renal tubule dysfunction with significant hypophosphatemia. If data from these 6 subjects are removed, data from the remaining 83 subjects in the All TDF cohort show mean Z-score declines that were much less: -0.24 SD, -0.25 SD and -0.08 SD at weeks 96, 120 and 144, respectively.

Table 12. Study GS-US-104-0352: Total Body Z-score – Change from baseline by treatment group (RAT)

	TDF (randomized phase) (N = 48)	d4T/ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Baseline (BL)			
N	47	48	88
Mean (SD)	-0.471 (1.20)	-0.386 (0.80)	-0.506 (1.02)
Week 24			
N	46	47	84
Mean Change from BL(SD)	-0.058 (0.27)	0.013 (0.24)	-0.059 (0.29)
Range	-0.65, 0.67	-0.53, 0.86	-0.88, 0.67
p-value: TDF vs. d4T/ZDV *	0.16		
# with increased Z-score	18	23	36
# with decreased Z-score	26	21	46
# with > 1 SD decrease in Z-score	0	0	0
Week 48			
N	41	45	82
Mean Change from BL (SD)	-0.193 (0.42)	-0.015 (0.40)	-0.158 (0.34)
Range	-0.94, 0.90	-1.3, 1.21	-0.94, 0.90
p-value: TDF vs. d4T/ZDV *	0.017		
# with increased Z-score	13	24	24
# with decreased Z-score	28	21	57
# with > 1 SD decrease in Z-score	0	1	0
Week 72			
N			71
Mean Change from BL (SD)			-0.198 (0.46)
Range			-1.4, 1.08
# with increased Z-Score			22
# with decreased Z-Score			49
# with > 1 SD decrease in Z-Score			1
Week 96			
N			64
Mean Change from BL (SD)			-0.338 (0.63)
Range			-2.26, 1.33
# with increased Z-Score			17
# with decreased Z-Score			47
# with > 1 SD decrease in Z-Score			8
Week 120			
N			30
Mean Change from BL (SD)			-0.469 (0.65)
Range			-2.42, 0.46
# with increased Z-Score			8
# with decreased Z-Score			22
# with > 1 SD decrease in Z-Score			7

	TDF (randomized phase) (N = 48)	d4T/ZDV (randomized phase) (N = 49)	All TDF (N = 89)
Week 144			
N			25
Mean Change from BL (SD)			-0.454 (0.89)
Range			-2.98, 1.05
# with increased Z-Score			9
# with decreased Z-Score			16
# with > 1 SD decrease in Z-Score			6
* p-value from Wilcoxon rank sum test Source: Tables 44.3, week 48 CSR; Table 44.7, week 96 CSR; ADDEXA dataset			

Total Body BMD: Age Subgroups

At baseline, younger children (age 2-5 y/o) had total body bone density that was above average as reflected by positive Z-scores at baseline, unlike this group's lumbar spine Z-scores and unlike those of older children (age 6-11 y/o) at both lumbar spine and total body. During the study however, both age groups showed an apparent negative effect of TDF on total body BMD and Z-scores, both relative to control in the randomized phase as well as during the extension phase. (Tables 13 and 14)

Table 13. Study GS-US-104-0352: Total Body BMD – Percent Change from baseline by age group* and treatment group (RAT)

	Age 2-5 y/o		Age 6-11 y/o	
	TDF (randomized phase) (N = 16)	d4T/ZDV (randomized phase) (N = 14)	TDF (randomized phase) (N = 28)	d4T/ZDV (randomized phase) (N = 34)
Baseline (BL)				
N	15	13	28	34
BMD, Mean (SD) (g/cm ²)	0.718 (0.06)	0.720 (0.06)	0.830 (0.06)	0.813 (0.06)
Z-score, Mean	0.181	0.111	-0.753	-0.578
Week 24				
N	13	13	28	33
Mean % change from BL(SD)	0.806 (1.74)	1.930 (2.11)	0.491 (2.01)	1.331 (1.07)
p-value: TDF vs. d4T/ZDV **	0.14		0.035	
# with > 4% decrease in BMD	0	0	1	0
Week 48				
N	11	12	27	32
Mean % change from BL (SD)	2.000 (1.92)	2.822 (3.84)	1.324 (2.47)	2.466 (2.08)
p-value: TDF vs. d4T/ZDV **	0.54		0.043	
# with > 4% decrease in BMD	0	1	1	0

	Age 2-5 y/o All-TDF (N = 24)	Age 6-11 y/o All-TDF (N = 59)
Week 48		
N	24	54
Mean % change from BL (SD)	1.962 (2.07)	1.458 (2.37)
# with > 4% decrease in BMD	0	1
Week 72		
N	21	46
Mean % change from BL (SD)	2.505 (2.58)	2.300 (3.72)
# with > 4% decrease in BMD	0	2
Week 96		
N	19	41
Mean % change from BL (SD)	4.142 (3.57)	3.059 (5.37)
# with > 4% decrease in BMD	0	3
Week 120		
N	9	18
Mean % change from BL (SD)	4.139 (2.36)	3.912 (6.33)
# with > 4% decrease in BMD	0	1
Week 144		
N	6	16
Mean % change from BL (SD)	4.665 (3.73)	6.032 (8.80)
# with > 4% decrease in BMD	0	1
Source: Table 43.4, Week 48 CSR; Table		
* Data not shown for 5 subjects who were age ≥12 y/o at baseline		

Table 14. Study GS-US-104-0352: Total Body Z-score – Change from baseline by age group* and treatment group (RAT)

	Age 2-5 y/o		Age 6-11 y/o	
	TDF (randomized phase) (N = 16)	d4T/ZDV (randomized phase) (N = 14)	TDF (randomized phase) (N = 28)	d4T/ZDV (randomized phase) (N = 34)
Baseline (BL)				
N	15	13	28	34
Mean (SD)	0.181 (1.3)	0.111 (0.54)	-0.753 (0.90)	-0.578 (0.81)
Week 24				
N	13	13	28	33
Mean Change from BL (SD)	0.042 (0.21)	-0.027 (0.40)	-0.090 (0.27)	0.016 (0.16)
Week 48				
N	11	12	27	32
Mean Change from BL (SD)	-0.303 (0.48)	-0.147 (0.59)	-0.124 (0.37)	0.016 (0.26)
	Age 2-5 y/o All-TDF (N = 24)	Age 6-11 y/o All-TDF (N = 59)		
Week 48				
N	20	57		
Mean Change from BL (SD)	-0.290 (0.43)	-0.111 (0.30)		

Week 72		
N	18	49
Mean Change from BL (SD)	-0.313 (0.55)	-0.159 (0.42)
Week 96		
N	17	43
Mean Change from BL (SD)	-0.605 (0.58)	-0.239 (0.63)
Week 120		
N	9	18
Mean Change from BL (SD)	-0.737 (0.44)	-0.382 (0.70)
Week 144		
N	6	16
Mean Change from BL (SD)	-0.852 (0.65)	-0.350 (0.96)
Source: Table 44.4, Week 48 CSR; Table 44.11, Week 96 CSR		
* Data not shown for 5 subjects who were age ≥ 12 y/o at baseline		

Total Body BMD: Gender Subgroups

The negative effects of TDF on total body BMD appeared to be somewhat more pronounced in male subjects. Within the All TDF cohort, changes from baseline total body Z-score were more negative in boys compared to girls at each timepoint. (Table 15)

Table 15. Study GS-US-104-0352: Total Body Z-score – Change from baseline by gender (All TDF cohort)

	Male (N=44)	Female (N=45)
Baseline (BL)		
N	44	44
Mean	-0.451	-0.561
Week 48		
N	42	40
Mean Change from BL	-0.205	-0.109
Week 96		
N	29	35
Mean Change from BL	-0.513	-0.194
Week 144		
N	11	14
Mean Change from BL	-0.683	-0.274
Source: ADDEXA dataset		

Summary of Bone Density Findings

In this study, similar to adolescents in the previous study (GS-US-104-0321), the HIV-infected subjects age 2-11 y/o had baseline bone density that was significantly below their age-matched peer group (i.e. negative Z-scores), with the exception of the younger (age 2-5 y/o) childrens' total body BMD. Baseline height and weight Z-scores were also negative, as in the adolescent study, and small bone size related to delayed growth is expected to contribute to lower BMD as measured by DXA.

The 2-11 y/o subjects in study GS-US-104-0352 received 8 mg/kg/day of TDF, mostly in a new powder formulation. A PK substudy showed systemic exposure that was somewhat lower than

historical exposure data in adults receiving the marketed 300 mg dose, unlike the adolescents previously, who received the adult dose and had comparable TDF exposure.

Unlike the adolescent study, where TDF appeared to have a negative effect on **lumbar spine BMD**, the 2-11 y/o children maintained their baseline spine Z-scores over 3 years of TDF exposure. Although the TDF group lagged slightly behind the control group at week 48, the differences were not significant, and both groups' Z-scores were slightly above baseline at that point. Boys and girls had equally favorable lumbar spine results. However, data for the older children (age 6-11 y/o) were somewhat less favorable than those of the younger children (age 2-5 y/o).

In contrast to lumbar spine findings, **total body BMD** clearly appeared to be negatively affected by TDF, i.e. more consistent with the adolescents' results. During the randomized phase, the TDF group had lower BMD gains than the control group at 24 and 48 weeks. This TDF/control difference was statistically significant for the overall study population as well as for the older (age 6-11 y/o) subgroup. This is unlike the previous adolescent study, where there were no statistical differences between TDF and control. In the extension phase of the new study, total body Z-scores declined progressively, unlike lumbar spine, but similarly to the previous adolescent study. Much of this decline for the overall All-TDF group was attributable to 6 of the 89 subjects who had more than one total body Z-score that was >1 SD below baseline between weeks 96-144; two of these 6 subjects had features suggestive of proximal renal tubule dysfunction with significant hypophosphatemia. Total body Z-score changes were somewhat more negative for boys compared to girls.

As in the adolescent study, body **height and weight** Z-scores were maintained through the study. *Reviewer's comment: Thus, TDF does not appear to affect bone growth in the overall treated group.*

Biochemical Markers of Bone Turnover

Serum N-telopeptide (NTX) and C-telopeptide (CTX) were measured in study GS-US-104-0352 as circulating indicators of bone resorption. Similar to the previous adult and adolescent studies, these markers appeared to increase from baseline somewhat more in the TDF group than the comparison group; the between-group difference was borderline-significant. (**Table 16**) Also similar to the previous studies, there were trends to return to baseline after the first year.

Table 16. Study GS-US-104-0352: Bone Resorption Markers (RAT)

	TDF (N=48)	d4T/ZDV (N=49)	p-value: TDF vs. Placebo*	All TDF (N=89)
Serum N-Telopeptide – Mean (SD), nM BCE				
Baseline	53.71 (22.47)	56.09 (18.90)	0.34	55.91 (21.32)
Change at Week 4	1.15 (21.43)	0.01 (20.27)	0.73	1.15 (21.43)
Change at Week 16	-0.65 (20.91)	-6.25 (20.37)	0.30	-0.65 (20.91)
Change at Week 24	5.05 (22.48)	-2.10 (25.63)	0.039	5.05 (22.48)
Change at Week 48	5.84 (27.27)	-0.45 (21.00)	0.27	5.84 (27.27)
	(↑ 10.8%)	(↓ 0.8%)		
Change at Week 96				-1.67 (26.17)
Change at Week 144				3.16 (32.07)

Serum C-Telopeptide – Mean (SD), ng/mL				
Baseline	1.972 (0.53)	2.012 (0.62)	0.56	2.140 (0.68)
Change at Week 4	0.295 (0.64)	0.166 (0.50)	0.28	0.295 (0.64)
Change at Week 16	0.330 (0.73)	0.156 (0.64)	0.35	0.330 (0.73)
Change at Week 24	0.288 (0.69)	0.097 (0.63)	0.24	0.288 (0.69)
Change at Week 48	0.569 (0.93)	0.250 (0.71)	0.090	0.569 (0.93)
	(↑ 28.8%)	(↑ 12.4%)		
Change at Week 96				0.035 (0.99)
Change at Week 144				0.072 (0.64)

* p-value from Wilcoxon rank sum test

Source: Week 48 CSR Tables 46.1 and 46.2, ADLAB dataset

Serum osteocalcin and bone-specific alkaline phosphatase (BSAP) were measured as indicators of bone formation. These markers were also consistent with previous adult and adolescent findings, showing increases during the first year of TDF that were significantly different from changes in the control group (Table 17). Among the 4 subjects with the greatest increase in BSAP were the 3 subjects with features of PRT dysfunction and hypophosphatemia (see below).

Table 17. Study GS-US-104-0352: Bone Formation Markers (RAT)

	TDF (N=48)	d4T/ZDV (N=49)	p-value: TDF vs. d4T/ZDV*	All TDF (N=89)
Serum Osteocalcin – Mean (SD), ng/mL				
Baseline	28.75 (8.85)	29.95 (8.94)	0.34	28.72 (10.08)
Change at Week 4	1.43 (8.57)	1.34 (8.61)	0.93	1.43 (8.57)
Change at Week 16	0.94 (8.65)	0.18 (8.02)	0.67	0.94 (8.65)
Change at Week 24	0.76 (8.49)	-1.04 (9.09)	0.16	0.76 (8.49)
Change at Week 48	1.67 (8.78)	-3.61 (9.72)	0.016	1.67 (8.78)
	(↑ 5.8%)	(↓ 12%)		
Change at Week 96				-7.58 (9.62)
Change at Week 144				-8.17 (11.55)
Serum Bone Specific Alkaline Phosphatase – Mean (SD), U/L				
Baseline	128.16 (42.57)	124.70 (47.68)	0.53	126.44 (45.13)
Change at Week 4	6.42 (26.18)	3.47 (24.29)	0.79	6.42 (26.18)
Change at Week 16	17.75 (33.45)	-0.32 (27.67)	0.03	17.75 (33.45)
Change at Week 24	18.91 (335.99)	-3.95 (34.84)	0.01	18.91 (35.99)
Change at Week 48	28.37 (40.68)	0.91 (28.06)	<.001	28.37 (40.68)
	(↑ 22%)	(↑ 0.7%)		
Change at Week 96				8.94 (60.00)
Change at Week 144				18.91 (111.98)

* p-value from Wilcoxon rank sum test

Source: Week 48 CSR Tables 46.3 and 46.4, ADLAB dataset

Parathyroid Hormone

There were modest increases in serum PTH in the tenofovir DF group and small decreases in the control group, similar to results in adolescents and adults. (Table 18) Differences between treatment groups in the change from baseline in PTH were statistically significant at Weeks 16, 24, and 48. However, mean values remained in the normal range in both groups; the subgroup of 3 subjects with features of proximal renal tubule (PRT) dysfunction/hypophosphatemia had minimal change in PTH; and the subgroup of 16 subjects who had >4% BMD loss at any point

had a mean PTH increase at week 48 of only 6.69 pg/mL, slightly less than the overall All TDF cohort; therefore clinical significance of these changes in PTH are unclear.

Table 18. Study GS-US-104-9352: Parathyroid Hormone (RAT)

Mean (SD), pg/mL				
	TDF (N=48)	d4T/ZDV (N=49)	p-value: TDF vs. d4T/ZDV*	All TDF (N=89)
Baseline	35.27 (15.73)	39.57 (25.46)	0.55	
Change at Week 4	1.57 (16.12)	-1.79 (15.57)	0.21	1.57 (16.12)
Change at Week 16	7.87 (12.92)	-5.54 (19.62)	0.0001	7.87 (12.92)
Change at Week 24	8.57 (16.92)	-5.65 (23.28)	0.0002	8.57 (16.92)
Change at Week 48	2.66 (17.70)	-8.19 (14.70)	0.0006	8.75 (19.97)
	(↑ 7.5%)	(↓ 2.1%)		
Change at Week 96				11.71 (21.86)
Change at Week 144				2.4 (16.06)
*p-value from Wilcoxon rank sum test Source: Week 48 CSR Table 46.5, ADLAB dataset				

25 OH Vitamin D

The median 25OH Vitamin D level was within the insufficiency range (21–29 ng/mL) at baseline for both groups. There were no significant differences between treatment groups in the change from baseline in 25OH Vitamin D at any time point in the randomized treatment period. (Table 19)

Table 19. Study GS-US-104-0352: 25OH Vitamin D (RAT)

Mean (SD), ng/mL				
	TDF (N=48)	d4T/ZDV (N=49)	p-value: TDF vs. d4T/ZDV*	All TDF (N=89)
Baseline	26.7 (11.4)	26.1 (10.2)	0.98	25.1 (10.4)
Change at Week 4	5.9 (11.2)	4.9 (9.7)	0.48	5.9 (11.2)
Change at Week 16	4.1 (9.8)	2.5 (7.8)	0.40	4.1 (9.8)
Change at Week 24	3.8 (11.0)	1.6 (9.3)	0.35	3.8 (11.0)
Change at Week 48	-1.4 (8.3)	-2.7 (13.2)	0.69	2.8 (9.8)
Change at Week 96				5.9 (8.5)
Change at Week 144				1.2 (10.3)
*p-value from Wilcoxon rank sum test Source: Week 48 CSR Table 46.6, ADLAB dataset				

Serum calcium

Mean baseline serum calcium was 9.4 mg/dL. Mean values were maintained within 0.1 mg/dL of baseline at all timepoints for both treatment groups within the initial 48 weeks. In the All TDF cohort, mean baseline serum calcium was 9.74 mg/dL and means at subsequent timepoints were mostly between 9.74 and 9.87 mg/dL.

In the randomized phase, no subjects had hypocalcemia; 15 subjects (10 TDF, 5 control) had mild (Grade 1) hypercalcemia (reference values varied by age group). In the All TDF cohort, there were 11/89 subjects with grade 1 hypercalcemia (max. 10.8 mg/dL) and no subjects with hypocalcemia.

Serum phosphorus

Reference ranges for serum phosphorus vary and decline from infancy to adulthood. In general, the LLN is approximately 4.5 mg/dL for infants, 3.5 mg/dL for children and 2.5 mg/dL for adults. This study used a published set of reference values which vary across multiple age and gender subgroups.

Mean baseline serum phosphorus levels were 4.96 mg/dL for the group randomized to TDF and 5.04 mg/dL for the group randomized to control. There was minimal change during the initial 48 weeks: -0.18 mg/dL (TDF) and -0.25 mg/dL (control) at week 48. During this phase, 2 TDF subjects had grade 1 hypophosphatemia (3.5 and 3.2 mg/dL) vs. 1 d4T/ZDV subject (3.0 mg/dL).

In the All TDF cohort of 89 subjects, as in the previous adolescent study, phosphorus levels declined after more than one year of TDF treatment, with mean changes of -0.23, -0.43 and -0.66 mg/dL at weeks 96, 120 and 144 respectively. There were 3 subjects (#9004, 9030, 9071) who experienced multiple readings of hypophosphatemia within the 2nd and 3rd years of TDF treatment along with other features consistent with proximal renal tubule (PRT) dysfunction, and 2 other subjects (#9045, 9046) with possible PRT dysfunction but only borderline low phosphate; these 5 subjects are discussed below. Other than these 5 subjects there were only 3 subjects who had any level (each had only one) < 3.5 mg/dL while receiving TDF: levels of 2.9 mg/dL at week 60 (this subject had baseline level 3.2 mg/dL), 3.3 mg/dL at week 72, and 3.4 mg/dL at week 144.

There was a total of 16 subjects (#9004, 9005, 9021, 9024, 9026, 9030, 9035, 9036, 9037, 9042, 9046, 9058, 9060, 9070, 9071, 9074) who had either lumbar spine or total body BMD that was >4% below baseline at at least one point. Other than the 5 subjects listed above, none of these 16 exhibited any significant trend toward hypophosphatemia during the study.

This reviewer dichotomized All-TDF subjects into those who had any serum phosphorus level <4.0 mg/dL (n=16) and those who did not (n=73), and then compared percent changes from baseline in BMD between the groups (**Table 20**). Unlike a similar comparison previously made in adolescent subjects in study GS-US-104-0321, the lower-phosphorus group did as well as the others in BMD gains.

Table 20. Study GS-US-104-9352: BMD – Percent Change from baseline (SD) by phosphorus groups* (All-TDF)

	Low-Phosphorus N=16	Normal-Phosphorus N=73
Lumbar Spine BMD		
Week 24 (n = 15, 69)	1.33 (3.70)	2.14 (4.08)
Week 48 (n = 16, 67)	4.75 (6.19)	4.04 (5.16)
Week 72 (n = 14, 58)	7.62 (10.15)	5.49 (6.73)
Week 96 (n = 12, 52)	10.89 (13.97)	9.30 (7.48)
Week 120 (n = 7, 23)	17.89 (16.89)	12.24 (5.87)
Week 144 (n = 7, 18)	19.67 (17.72)	15.82 (7.93)

Total Body BMD		
Week 24 (n = 15, 69)	0.14 (1.96)	0.93 (2.05)
Week 48 (n = 15, 67)	1.64 (2.98)	1.65 (2.15)
Week 72 (n = 13, 58)	2.53 (4.63)	2.52 (3.22)
Week 96 (n = 12, 52)	2.57 (7.73)	3.81 (4.13)
Week 120 (n = 7, 23)	4.55 (10.87)	4.51 (2.98)
Week 144 (n = 7, 18)	5.23 (13.28)	6.61 (4.80)
*Low-phosphorus = subjects with at least one level < 4.0 mg/dL; Normal-phosphorus = subjects without any level < 4.0 mg/dL Source: ADLAB and ADDEXA datasets		

Serum magnesium

During the 48-week randomized phase, grade 1 hypomagnesemia was reported for 10 TDF subjects and 15 d4T/ZDV subjects. In the All TDF cohort, there were 27/89 subjects with grade 1 hypomagnesemia.

Adverse Events related to bone

There were no fractures or other “bone events” reported for any subject receiving TDF up to the data cut-off date for the week 96 interim study report. During the randomized phase, one TDF subject experienced an unspecified “limb injury” and one control subject receiving ZDV was reported with a “bone nodule in right arm and left trunk” on day 9, considered nonserious, with no further details.

Bone data in subjects with evidence of proximal renal tubule disorders

The Applicant analyzed laboratory data to identify subjects with features suggestive of a TDF-related proximal renal tubule (PRT) disorder similar to those identified in postmarketing reports. The criteria specified Grade 1 or higher abnormality of at least 2 out of 5 parameters (proteinuria, glycosuria, hypophosphatemia, low serum bicarbonate, hypokalemia) as well as >35% reduction from baseline in creatinine clearance. There were 5 subjects who met these PRT dysfunction criteria and are discussed below; 4 of these were considered AEs (3 for hypophosphatemia, 1 for glycosuria), and they accounted for all 4 of the AEs resulting in discontinuation from this study at the time of data cutoff for the week 96 study report.

- **Subject 9004:** an 11 y/o black male randomized to TDF, had normal renal parameters until after week 60 when serum phosphorus dropped to 3.2 mg/dL (from baseline 5.0 mg/dL). From week 108 to week 157 his phosphorus level remained low (max Grade 3) with most levels between 1.8-2.6 mg/dL, and he was not given phosphate supplementation as required by the protocol. He had mild declines in serum potassium and bicarbonate and mild proteinuria as well, but no decline in creatinine clearance. His serum BSAP rose from baseline 108.9 U/L to 569 U/L at week 147 with serum alkaline phosphatase increasing from baseline 251 U/L to 1306 U/L (reference 74-390 U/L) with increases from baseline in osteocalcin, NTX and CTX of 33%, 50% and 53%, respectively. There was minimal change in PTH, 25OH vitamin D, calcium, magnesium or LFTs. This was reported as an AE of **hypophosphatemia** and TDF was discontinued at week 146; serum phosphorus recovered to 3.1 and 3.3 mg/dL at weeks 153 and 157. This subject entered the study with low BMD Z-scores of -1.36 (lumbar spine) and -1.429 (total body). During the study he had pronounced declines from baseline in BMD of -13.79% (lumbar spine) and -18.01% (total body) at week 144, resulting in week 144 Z-scores of -3.19 (lumbar spine) and -4.41 (total body).

- Subject 9030:** a 10 y/o white female randomized to TDF, had onset at week 48 of low serum bicarbonate and potassium, later followed by moderate proteinuria and decline in creatinine clearance and hypophosphatemia (from baseline phosphorus = 5.0 mg/dL). Except for one reading the serum phosphorus was low (1.8-3.0 mg/dL, max Grade 3) between week 96 and week 156, and there was only mild increase (from 2.2 to 2.9 mg/dL) when phosphate supplementation was given starting at week 137. This subject's serum BSAP increased from baseline 116.1 U/L to 277.6 U/L at week 144; serum alkaline phosphatase increased from baseline 252 U/L to ~450-600 U/L between weeks 12-144. Her serum osteocalcin, NTX and CTX increased from baseline to week 48 by 49%, 130% and 196% respectively; however, these parameters returned to near baseline at weeks 96 and 144. There was minimal change in PTH and calcium. This was reported as an AE of **hypophosphatemia** and TDF was discontinued at week 153; the final serum phosphorus was 2.6 mg/dL at week 157. This subject entered the study with low BMD Z-scores of -1.83 (lumbar spine) and -1.36 (total body). During the study she experienced lumbar spine BMD increase from baseline of 12.04% but total body BMD decline from baseline of -3.36% (week 144). Both Z-scores declined and at week 144 were -2.62 (lumbar spine) and -2.94 (total body).
- Subject 9045:** a 15 y/o Mestizo male randomized to TDF, experienced moderate decline in creatinine clearance and mild/intermittent proteinuria, glycosuria and low serum bicarbonate. His serum phosphorus was 5.8 mg/dl (high) at baseline and gradually declined to 3.3 mg/dL at week 96 and a minimum of 2.4 mg/dL (borderline-low for 15 y/o) at week 192. These abnormalities were not reported as an AE and TDF was not discontinued. This subject entered the study with low BMD Z-scores of -2.62 (lumbar spine) and -2.92 (total body). During the study he experienced substantial increases in BMD of 22.28% (lumbar spine) and 11.50% (total body) from baseline to week 144. His final Z-scores improved modestly to -2.14 (lumbar spine) and -2.86 (total body) at week 144.
- Subject 9046:** a 9 y/o Mestizo male randomized to continue baseline treatment (ZDV) had normal labs until, at week 72 of All-TDF cohort, he had onset of glycosuria (Grade 3-4), proteinuria (Grade 1-2), and moderate decline in creatinine clearance. This persisted and a renal biopsy at week 83 was "normal by light microscopy". TDF was discontinued from week 84 to week 88 with improvement in labs, followed by recurrent glycosuria upon rechallenge, then resolution after permanent drug discontinuation at week 100. This subject's serum phosphorus remained normal except for borderline (3.5-3.6 mg/dL) readings at weeks 96-100. AEs of **glycosuria** and **chronic renal failure** were reported. This subject began TDF treatment with normal BMD Z-scores of -0.09 (lumbar spine) and -0.10 (total body). During the study he experienced declines from baseline to week 100 of -4.28% (lumbar spine) and -0.23% (total body), resulting in Z-scores at week 100 of -0.69 (lumbar spine) and -0.72 (total body).
- Subject 9071:** a 9 y/o Native American male randomized to TDF, had normal labs until week 48 onset of hypophosphatemia, followed by decline in creatinine clearance with mild proteinuria, glycosuria, hypokalemia and low serum bicarbonate. His serum phosphorus ranged between 1.6 and 3.2 mg/dL from week 48 through week 84 when TDF was discontinued; the level recovered to 3.7 mg/dL at week 90. Phosphate supplementation from week 80 to week 84 did not increase the level. This subject had increases in serum BSAP from baseline 114.6 U/L to 214 U/L at week 24 and 186 U/L at week 48; serum alkaline phosphatase increased from baseline 255 U/L to 474 U/L at week 72 followed by decline to baseline at week 96. Serum PTH, osteocalcin, NTX and CTX also increased moderately from baseline. This was reported as an AE of **hypophosphatemia**. This subject began the study with low BMD Z-scores of -1.4 (lumbar spine) and -0.2 (total body). During the study he experienced BMD declines from baseline at week 96 of -5.03% (lumbar spine) and -4.41% (total body). Z-scores at week 96 were -2.1 (lumbar spine) and -1.6 (total body). This subject was on concomitant medications of sertraline, risperidone, divalproex, methylphenidate and

dexmethylphenidate for depression, migraine headaches and ADHD. These medications preceded the study and were continued through the study.

In summary, there were 3 subjects (#9004, 9030 and 9071) who had multiple subnormal serum phosphorus levels, including some <2.0 mg/dL, along with other features suggestive of PRT dysfunction. The abnormalities tended to appear after about 1 year of TDF therapy and then persist; phosphorus levels remained low, even with supplementation, until TDF was discontinued. All 3 of these subjects had increases in markers of bone turnover particularly BSAP which increased 5-fold in subject 9004, who was the subject with the most pronounced hypophosphatemia as well as bone loss. All 3 of these subjects experienced declines in BMD Z-scores of both lumbar spine and, especially, total body that were greater than the mean of the overall study population. In 2 of these 3 subjects (#9004, 9030), Z-score declines were apparent in the first year of therapy, predating any significant drop in serum phosphorus. There were insufficient follow-up data on these 3 subjects to assess recovery of serum phosphorus, alkaline phosphatase or BMD following TDF discontinuation. The other 2 subjects with possible PRT dysfunction (#9045, 9046) had only borderline hypophosphatemia, and experienced milder decline in BMD Z-scores (#9046) or improved BMD Z-scores (#9045).

Discussion and Conclusions

In adults, several studies have shown that initiation of antiretroviral therapy is associated with a decline in BMD of 2-6%, mostly within the first 6-12 months, and that this decline is greater with regimens that include TDF. However, BMD stabilizes after 1-2 years even with continued TDF therapy, and it is unknown whether fracture risk is affected.

Pediatric Written Request controlled studies involving TDF in adolescents (age 12-17, study 0321), and now in younger children (age 2-11, study 0352, current NDA) as well, also appear to show an effect of TDF on bone density. In both adolescents and younger children, the groups receiving TDF experienced lower than the expected rate of increase in total body BMD over 2-3 years, as shown by a decline in BMD Z-score, although linear bone growth continued at the expected rate. Among younger children (age 2-11), boys had total body Z-scores that declined more than those of the girls. Lumbar spine BMD was also negatively affected by TDF in adolescents, although this did not appear to apply to the younger children, particularly the 2-5 y/o age group. Biochemical markers of bone turnover (formation and resorption) as well as serum PTH tended to increase from baseline during TDF treatment in both pediatric and adult age groups.

These negative effects of TDF on bone density have, in general, occurred in subjects with no evidence to suggest the type of renal tubule dysfunction and possible osteomalacia or rickets that were seen in the postmarketing reports or the studies in monkeys. However in the current study, 3 out of 89 All-TDF subjects (ages 9, 10 and 11 y/o) had multiple readings of hypophosphatemia (resulting in study discontinuation for all 3) as well as other features consistent with proximal renal tubule dysfunction. All 3 of these children had major declines in BMD Z-scores; one had the greatest BMD declines, by a large margin, of any subject in the study (-13.79% lumbar spine and -18.01% total body).

A similar patient (11 y/o girl) in a published prospective study¹ experienced a 20% decline in BMD after only 12 weeks of TDF, and a 27% decrease after 24 weeks, along with a decline in serum phosphorus from 5.2 to 3.4 mg/dL; her BMD changes reversed after stopping TDF.

Bone biopsies have not been performed on any of the subjects from the TDF clinical trials or the postmarketing reports. Biopsy data would show whether TDF causes osteoporosis-like effects on bone (decreased bone volume and altered microarchitecture), or osteomalacia effects (inadequate mineralization), or both, which may help delineate a mechanism (direct effects on bone cells vs. indirect effects through kidney). There are also minimal urine chemistry data available for TDF therapy (e.g. to rule out renal phosphate leak). However, a postmarketing required study in HBV-infected adolescents receiving TDF is currently collecting such data to determine whether changes in BMD and/or bone metabolism markers correlate with any renal tubule effects of the drug. This knowledge is needed to devise approaches to managing this toxicity.

Labeling

After review of the available interim data, we recommend the following labeling changes:

Section 5.6 Decreases in Bone Mineral Density

The first paragraph in this section is proposed by the Applicant to have only one change (in red) related to the expanded pediatric age group:

Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients ~~12 years of age and older~~ who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

The second paragraph describing effects on adult bones has no proposed changes.

The third paragraph describing effects on pediatric bones is proposed by Applicant to have the following changes (in red). This reviewer considers these labeling changes to be acceptable, and also suggests one additional change in blue.

In ~~a~~ clinical studies ~~of evaluating VIREAD in HIV-1 infected pediatric subjects 12 2 to <18~~ years of age ~~and older (Study 321)~~, bone effects were similar to those observed in adult subjects. Under normal circumstances BMD increases rapidly in ~~this age group~~ pediatric patients. In Study 352 (2 to <12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the VIREAD and the d4T or AZT treatment groups. Total body BMD gain was less in the VIREAD compared to the d4T or AZT treatment group. One VIREAD-treated subject and no d4T or AZT-treated subject experienced significant (>4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with VIREAD for 96 weeks. Three subjects with substantial bone loss during this study also exhibited hypophosphatemia and other features suggestive of proximal renal tubule dysfunction. In ~~this study~~ Study 321 (12 to <18 years), the mean rate of bone BMD gain at Week 48 was less in the VIREAD-treated group compared to the placebo treatment group. Six VIREAD treated subjects and one placebo treated subject had significant

(>4%) lumbar spine BMD loss ~~in 48 weeks at Week 48. Among 28 subjects receiving 96 weeks of VIREAD, Changes from baseline in BMD Z-scores declined by were~~ -0.341 for lumbar spine and -0.458 for total body ~~in the 28 subjects who were treated with VIREAD for 96 weeks. In both studies, Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults.~~

The concluding paragraphs are proposed to remain unchanged:

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD [See Adverse Reactions (6.2)].

The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

References

1. Purdy J, Gafni RI et al, Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus, *J. Pediatr.* **152** (2008), pp. 582-584.
2. Giacomet V et al, A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children, *J. Acquir. Immune Defic. Syndr.* **40** (2005), pp. 448-450.
3. Kalkwarf HJ et al, The Bone Mineral Density in Childhood Study: bone mineral content and density according to age, sex, and race, *JCEM*: **92** (2007), pp. 2087-2099.
4. Zemel BS et al, Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the Bone Mineral Density in Childhood Study, *JCEM*: epub 9/14/11, doi:10.1210/jc.2011-1111

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

/s/

STEPHEN R VOSS
11/28/2011

THERESA E KEHOE
11/29/2011

AUDREY L GASSMAN
11/29/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 022577 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type
Proprietary Name: tenofovir disoproxil fumarate oral powder Established/Proper Name: VIREAD Oral Powder Dosage Form: oral powder Strengths: 40 mg / gram of powder		
Applicant: Gilead Sciences Agent for Applicant (if applicable):		
Date of Application: June 16, 2011 Date of Receipt: June 16, 2011 Date clock started after UN: July 18, 2011		
PDUFA Goal Date: January 18, 2011		Action Goal Date (if different):
Filing Date: September 16, 2011		Date of Filing Meeting: July 11, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): New oral powder dosage form intended for pediatric patients ages 2 to less than 12.		
Type of Original NDA: Type 3 AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: Response to pediatric WR	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 52,849 / NDA 21356				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid (after Unacceptable for Filing) <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 773 1486">Drug Name</th> <th data-bbox="773 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	X			
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: Consult sent to Division of Reproductive and Urologic Products on 8/11/11 for review of bone metabolism data.</i>	X			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 29, 2010 and June 15, 2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 11, 2011

BLA/NDA/Supp #: 22577

PROPRIETARY NAME: Viread® Oral Powder

ESTABLISHED/PROPER NAME: tenofovir disoproxil fumarate

DOSAGE FORM/STRENGTH: oral powder, 40 mg / gram of powder

APPLICANT: Gilead Sciences, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND:

NDA 22577 for VIREAD (tenofovir disoproxil fumarate) Oral Powder was submitted on June 16, 2011. The application was decided to be unacceptable for filing, as no user fee was received (the applicant claimed a fee exemption for orphan designation for pediatric patients 16 and under, which was not acceptable due to the fact that the proposed labeling contains indications which do not fall under the orphan designation for pediatric patients). The sponsor submitted a full user fee on July 18, 2011 and the review clock was re-started.

The application was submitted in response to the FDA's written request for pediatric studies (to NDA 21356, as last amended on September 16, 2010), along with a request for pediatric exclusivity determination.

A CMC supplement was also submitted to NDA 21356 to provide reduced-strength Viread tablets (150-, 200-, and 250-mg strength) for pediatric patients who weigh 17 to less than 35 kg and are able to swallow tablets. That supplement references the clinical data and proposed labeling submitted in NDA 22577.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Katherine Schumann	Y
	CPMS/TL:	Victoria Tyson	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Clinical	Reviewer:	Tafadzwa Vargas-Kasambira	Y

	TL:	Linda Lewis	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Narayana Battula	N
	TL:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Dionna Green	Y
	TL:	Sarah Robertson	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Guoxing Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rao Kambhampati	Y
	TL:	Stephen Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Arzu Selen, Biopharmaceutics		Y
Other attendees	Brantley Dorch, OSE Project Manager Jeannie David, ONDQA Project Manager		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: For PK and bioequivalence data only</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jeffrey S Murray, M.D., M.P.H., Deputy Director, DAVP	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Filing Date: September 16, 2011 Mid-Cycle Meeting: October 18, 2011 Wrap-Up Meeting: December 21, 2011 Primary Reviews Due: December 25, 2011 Secondary Review Due: December 28, 2011 CDTL Review Due: January 4, 2012 Labeling and PMR/PMC/REMS discussions: December 28, 2011 Action Date: January 18, 2012	
Comments: Milestones shifted due to re-start of PDUFA clock on July 18, 2011 (unacceptable for filing – user fees).	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter (Note: PLR format comments sent for Viread label with NDA 21356 / S-37)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

KATHERINE SCHUMANN
08/11/2011