CLINICAL REVIEW

Application Type	NDA/sNDA
Application Number(s)	NDA 22577/sNDA 21356
Priority or Standard	P
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Reviewer Name(s)	Tafadzwa Vargas-Kasambira, M.D., M.P.H.
Review Completion Date	December 18, 2011
Established Name	Tenofovir disoproxil fumarate
(Proposed) Trade Name	VIREAD®
Therapeutic Class	Antiretroviral drug
Applicant	Gilead Sciences
Formulation(s)	Oral powder and reduced-strength tablets
Dosing Regimen	Tablets: For pediatric patients weighing ≥ 17 kg (≥ 37 lb) who can swallow an intact tablet, one VIREAD tablet (150, 200, 250 or 300 mg based on body weight) once daily orally without regard to food Oral powder: 8 mg/kg VIREAD oral powder (up to a maximum of 300 mg) once daily with food
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	Pediatric patients 2 to < 12 years of age

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1.1 Recommendation on Regulatory Action

NDA 22577 and supplement to NDA 21356 (submission number 38) containing interim data from the pediatric clinical trial GS-US-104-0352 support the indication for use of Viread® (tenofovir disoproxil fumarate) in combination with other antiretroviral drugs for the treatment of HIV-1 infection in pediatric patients 2 to less than 12 years of age. This reviewer recommends the approval of the NDA and supplemental NDA (sNDA), submission number 38. Tenofovir disoproxil fumarate (TDF, Viread), in combination with other antiretroviral drugs, resulted in reduction in HIV-1 RNA viral load, and relatively minor increases in CD4 cell counts, over the 48 week study period across all ages studied.

Through the review of this NDA and sNDA, no deficiencies that would preclude the approval of this submission were identified. TDF was studied in a single Phase III, randomized, open-label trial that enrolled 97 pediatric subjects 2 years to less than 12 years of age (of whom 92 received the to-be-marketed dose) with documented HIV-1 infection who were virologically suppressed (plasma HIV-1 RNA < 400 copies/mL) at baseline on a stavudine (d4T)- or zidovudine (ZDV)-containing highly active antiretroviral therapy (HAART) regimen. The trial compared the safety and efficacy of switching d4T or ZDV to TDF, for a 48-week period. The initial 48 weeks of the trial consisted of a randomized, open-label, parallel-group treatment period. Eligible subjects were randomized in a 1:1 ratio to either replace d4T or ZDV with TDF (Treatment Group A) or to continue stavudine (d4T) or zidovudine (ZDV) (Treatment Group B) on their existing HAART regimen for 48 weeks. Randomization was stratified by whether a subject was currently on d4T or ZDV. Subjects who completed 48 weeks of randomized treatment who continued to be less than 18 years of age were given the option to either continue or initiate TDF in the first of two 96-week trial extensions (collectively referred to as the extension phase), if the switch was deemed beneficial for the subject. After completion of the first 96-week trial extension, currently enrolled subjects who were benefitting from TDF and remained < 18 years of age were given the option to continue to receive TDF for an additional 96 weeks.

The applicant's proposed dose for Viread oral powder was 8 mg/kg per day, and the rationale for this dose was based on the results from two previously conducted pilot trials. The PK results from both these trials (926 and 927) suggested that this dose of Viread oral powder in children < 12 years of age appeared to approximate effective adult exposures, although exposures were slightly lower than adult exposures. The steady-state AUC_{tau} for tenofovir DF from historical adult data from previously completed trials showed that at the 28^{th} dose (~Week 4) AUC_{tau} was 3020 ng.hr/mL. The overall AUC_{tau} in Trial 0352 was 2586.3 ng.hr/mL. The mean difference in AUC_{tau} between adults and pediatric subjects was approximately 11.2% for subjects 2 to < 6 years of age, and 12.5% for subjects 6 to < 12 years of age. The mean differences in the pediatric

AUC_{tau} in both age groups were not great, and one may conclude, therefore, that the exposure in pediatric subjects approximated that in adult subjects.

Tenofovir DF adult tablets and oral powder, in combination with other antiretroviral agents, demonstrated good antiviral activity over the 48 week trial period. Overall, 89% of subjects in the TDF group, and 90% of subjects in the d4T or ZDV group achieved an HIV RNA level < 400 copies/mL at Week 48. The criteria were met for noninferiority of TDF for the difference in the efficacy between the two groups using the FDA's preferred analysis method. However, the pre-specified primary endpoint of noninferiority of TDF for this difference was not met using an older method of efficacy analysis. The virologic response in this pediatric population was greater than one would expect in a treatment-experienced adult population using TDF, and similar to adult treatment-naïve populations.

The virologic response with TDF is robust in comparison with that of darunavir seen in pediatric subjects in a randomized, open-label trial that enrolled treatment-experienced pediatric subjects 6 to < 18 years, in which the proportion of subjects with HIV RNA < 400 copies/mL was 64% after 24 weeks. In an open-label, multicenter trial involving the use of Kaletra (lopinavir/ ritonavir), in both treatment-naïve and treatment-experienced subjects, the proportion of subjects who achieved and sustained an HIV-1 RNA < 400 copies/mL was 71 percent in treatment-experienced subjects and 80% in treatment-naïve subjects..

Additional efficacy analyses were conducted for this pediatric trial, including subgroup analyses by age, race, gender, and baseline CD4 percentage. There were slight differences in efficacy based on gender and race (slightly higher in males and in Whites), and the reasons for this are unclear. Adult data do not suggest that race or gender are associated with virologic efficacy of TDF, and these differences may have occurred by chance or may be due to small sample size. This reviewer concludes that there were no significant differences in virologic response rate between the subgroups that might be of concern.

The applicant demonstrated an acceptable safety profile for TDF. Overall adverse events in this pediatric population were common (85%), while serious adverse events were uncommon (four SAEs in four subjects), and none required discontinuation of trial drug from Week 0 to Week 48 of the trial period. A substantial number of adverse events were due to underlying disease conditions and common childhood illness, particularly routine childhood infections. Clinically significant laboratory events were infrequent, and did not lead to trial drug discontinuation during the first 48 weeks of study therapy. In general, the nature of adverse events in these pediatric subjects was similar to that of adult subjects noted previously.

This submission supports the approval of two new Viread dosing forms, namely the oral powder, and the reduced strength tablets (150 mg, 200 mg, and 250 mg). The Agency initially had concerns about the oral powder given its texture and the fact that it was unpalatable; there was concern that the formulation might not be well-tolerated in older or larger children, who would have to take a large volume of the drug, based on their weight. The reduced-strength tablets were

developed to address this problem, and are likely to be more appropriate for older children who can reliably swallow tablets.

This reviewer recommends the approval of Viread oral powder for use in HIV-1 infected children 2 to < 12 years of age, and the approval of the reduced strength Viread tablets (150 mg, 200 mg, and 250 mg) and the marketed 300 mg tablet for children who weigh ≥ 17 kg and can swallow a tablet. The oral powder formulation should be weight-based (8 mg/kg per day, up to a maximum of 300 mg per day).

1.2 Risk Benefit Assessment

Tenofovir DF is a nucleotide reverse transcriptase inhibitor (NRTI) that is currently approved for marketing in adults and in pediatric patients down to age 12 years. Given the relative paucity of effective and palatable antiretroviral drug options for children infected with HIV, approval of Viread oral powder and reduced strength tablets would fulfill a recognized need in this patient population. Virologic response has been demonstrated in this pediatric trial using a new formulation of Viread (oral powder) over a 48-week treatment period, with evidence of durability to at least 96 weeks.

Although the reduced strength tablets have not been studied in a clinical trial, they have the same composition as the marketed 300 mg tablet and similar dissolution properties. Efficacy was in general consistent across age groups and in various subgroups, although a slightly greater virologic response was found in males compared with females, and in Whites compared with Blacks. These discrepancies are not thought to be clinically relevant. Immunologic success was also demonstrated in this trial, with a substantial increase in CD4 count and percent over the 48-week treatment period.

A virology genotyping substudy conducted on 19/89 subjects (data available on 17 subjects; 5 in TDF group, 12 in d4T or ZDV group) who discontinued the trial due to virologic failure, or who had HIV RNA ≥ 400 copies/mL at Weeks 48, 96, and 144, or upon early discontinuation, demonstrated a very low level of resistance, with one subject having two substitutions, K65R and Y181C, and experiencing an early increase in HIV viral load before discontinuing the trial after Week 4. The pattern of resistance was consistent with the use of TDF or the concomitant antiretroviral drugs that the subject had previously taken.

Tenofovir DF was generally safe and tolerable in pediatric subjects in this trial. No deaths occurred during the randomized or extension periods. Many subjects experienced adverse events, though a much lower proportion experienced serious adverse events, or Grade 3 or 4 clinical or laboratory events. No adverse events led to trial drug discontinuation during 48 weeks of randomized therapy. Adverse events of special interest with the use of antiretroviral agents such as TDF (renal or bone events) occurred with low frequency, and no new safety signals, as compared with the adult TDF safety profile, were identified. There were, however, three subjects who developed substantial bone loss and hypophosphatemia and other features suggestive of

proximal tubular dysfunction. This highlights the need for careful monitoring of TDF during long-term use.

This reviewer supports approval of Viread oral powder for HIV-1 infected pediatric patients 2 to less than 12 years of age, and Viread reduced strength tablets (150 mg, 200 mg, and 250 mg) and the marketed 300 mg tablet. The applicant has provided an adequate amount of data to demonstrate that TDF is safe for use in the pediatric population as per the proposed indication. Review of the submitted data support the applicant's assertion that potential benefit of TDF use outweighs the potential risk.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Postmarket Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will submit periodic safety reports for review. The Viread label already contains a Patient Package Insert which was updated with pictorial/diagram instructions for dosing the powder formulation.

1.4 Recommendations for Postmarket Requirements and Commitments

A Postmarket Risk Evaluation and Mitigation Strategy (REMS) will not be required. No new PMRs or PMCs were established based on review of this trial. The applicant will submit periodic safety reports for review.

2 Introduction and Regulatory Background

2.1 Product Information

- Name: Tenofovir disoproxil fumarate (tenofovir DF, TDF, Viread®)
- Description: Oral powder is white, taste-masked, microencapsulated granules
- Chemical Class: *(R)*-9-[2-(phosphonomethoxy)propyl]adenine
- Molecular Formula: $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$
- Pharmacological Class: Nucleotide reverse transcriptase inhibitor (NRTI)
- Proposed Indication and Dosing: Treatment of HIV-1 infection in pediatric patients 2 to < 18 years of age, in combination with other antiretroviral drugs

  Tablets: for pediatric patients weighing ≥17 kg (≥37 lb) 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

Oral powder: 8 mg/kg VIREAD oral powder (up to a maximum of 300 mg) once daily with food.

Dosage Forms and Strengths:
Tablets: 150, 200, 250, and 300 mg
Oral Powder: 40 mg per 1 g of oral powder.

Table 1 and Table 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		**Oral Powder Once Daily**
Kilogram (kg)	**Pound (lbs)**	**Scoops of Powder**
10 to < 12	22 to < 26	2.0
12 to < 14	26 to < 31	2.5
14 to < 17	31 to < 37	3.0
17 to < 19	37 to < 42	3.5
19 to < 22	42 to < 49	4.0
22 to < 24	49 to < 53	4.5
24 to < 27	53 to < 60	5.0
27 to < 29	60 to < 64	5.5
29 to < 32	64 to < 71	6.0
32 to < 34	71 to < 75	6.5
34 to < 35	75 to < 77	7.0
≥ 35	≥ 77	7.5

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

Body Weight		
Kilogram (kg)	**Pounds (lbs)**	**Tablets Once Daily**
17 to < 22	37 to < 49	150 mg
22 to < 28	49 to < 62	200 mg
28 to < 35	62 to < 77	250 mg
≥ 35	≥ 77	300 mg

Medical Officer comment: Only kilogram (kg) units will be displayed in the label, according to Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) recommendations.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current indications are for the treatment of HIV-1 infection in adults and adolescents, and chronic hepatitis B infection in adults. As of October 2011, a total of 21 drugs have been approved for the HIV-1 treatment indication in the United States. The currently approved drugs for treatment of HIV-1 infection are described specifically in Table 3:

Table 3. Currently Available Treatment of HIV-1 Infection in Children

Brand Name	Generic Name	Pediatric Age with Use Labeling
NRTI		
Combivir®	lamivudine and zidovudine	>12 yr
Emtriva®	Emtricitabine, FTC,	≥ 0-3 months old
Epivir®	lamivudine, 3TC	≥3 months old
Retrovir®	zidovudine, AZT, ZDV	≥ 4 weeks old
Truvada®	tenofovir disoproxil/emtricitabine	≥ 12 years old
Videx EC®	enteric coated didanosine	
Videx®	didanosine, ddI,	≥ 2 weeks old
Viread®	tenofovir disoproxil fumarate, TDF	≥ 12 years old
Zerit®	stavudine, d4T	≥ Birth
Ziagen®	abacavir	≥ 3 months old
NNRTI		
Sustiva®	Efavirenz, EFV	>3 years old
Viramune®	Nevirapine, NVP	≥ 14 days old
PI		
Aptivus®	Tipranavir	≥ 2 years old
Kaletra®	lopinavir and ritonavir	≥ 4 weeks old
Lexiva®	Fosamprenavir Calcium	≥ 2 years old
Norvir®	ritonavir	>1 month old
Prezista®	Darunavir, DRV	≥ 6 years old
Reyataz®	atazanavir sulfate, ATV	≥ 6 years old
Viracept®	nelfinavir mesylate, NFV	≥ 2 years old

Brand Name	Generic Name	Pediatric Age with Use Labeling
Fusion Inhibitor		
Fuzeon®	enfuvirtide, T-20	≥ 6 years old
Entry Inhibitor		
Selzentry®	maraviroc	≥ 16 years old
Integrase strand transfer Inhibitor		
Isentress®	Raltegravir, RAL	≥ 16 years old

2.3 Availability of Proposed Active Ingredient in the United States

Tenofovir disoproxil fumarate, the active ingredient in Viread, is available in the United States by prescription only. The proposed API for the treatment of HIV-1 infected pediatric subjects will be the same as the approved tenofovir disoproxil fumarate. Patients who weight 17 kg or greater and can swallow an intact tablet, will take one of the new reduced strength tablets, based on body weight (150, 200, 250 mg) or the currently marketed 300 mg tablet. Patients who are unable to swallow tablets will take Viread oral powder up to a maximum dose of 300 mg. It is not anticipated that there will be any difficulty accessing the proposed pediatric formulations.

2.4 Important Safety Issues With Consideration to Related Drugs

Pertinent safety issues applicable to Viread include renal impairment and decreases in bone mineral density (BMD), as well as lactic acidosis and severe hepatomegaly with steatosis, fat redistribution, and immune reconstitution syndrome (IRIS) which have been associated with the NRTI class of drugs. Discontinuation of Viread has been associated with severe acute exacerbation of hepatitis,

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Viread was approved for treatment of HIV-1 infection in adults, in combination with other antiretroviral drugs (ARVs) on October 26, 2001. On March 24, 2010, Viread was approved for use in pediatric patients > 12 years (Efficacy supplement, NDA 21-356/S-033), on the basis of findings from Trial GS-US-104-0321: A phase III, randomized, double-blind, placebo-controlled study of the safety and efficacy of tenofovir DF as part of an optimized antiretroviral regimen in HIV-1 infected adolescents.

A Pediatric Written Request (PWR) was issued on December 21, 2001. Provisions included: two types of trials required (multiple-dose PK, safety, and activity trials, and randomized safety and activity trials, both in ARV therapy-experienced pediatric patients, with the latter at least through 48 weeks. Three trial objectives were stated: (1) determine PK and safety profile of TDF across

age range studied; (2) identify appropriate dose(s) for use in HIV-1 infected pediatric patients; and (3) evaluate activity of dose(s) in treatment regimens. Reports of requested pediatric trials were to be submitted on or before August 30, 2011. The PWR was amended on October 29, 2004, December 12, 2004, January 29, 2008, and September 14, 2009.

Trial GS-US-104-0352 was initiated on December 28, 2006 in pediatric subjects 2 to < 12 years of age. The trial was titled: A phase III, randomized, open-label trial comparing the safety and efficacy of switching stavudine or zidovudine to tenofovir DF versus continuing stavudine or zidovudine in virologically suppressed HIV-infected children taking highly active antiretroviral therapy.

On July 30, 2009, a Type B, pre-NDA meeting was held regarding the sponsor's planned September 2009 filing of a pediatric NDA for Viread oral powder for HIV-1 infection. Of concern to DAVP was the failure of Study 0352 to achieve the primary efficacy endpoint, namely the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48. The dose of 8 mg/kg of Viread oral powder (up to 300 mg) was based on earlier studies. Results showed the following: steady-state TDF exposures were similar between adolescents (Trial 0321) and younger pediatric subjects (Trial 0352); mean AUC_{tau} exposures in Trial 0352 were approximately 11% and 18% lower in children aged 2 to < 6 years and 6 to < 12 years, respectively; and the trial did not meet criteria for treatment non-inferiority at Week 48, based on ITT analysis. Gilead agreed to file the two trials separately and submit Week 96 data in Trial 0352, and data supporting 8 mg/kg dose of TDF in ages 2-12 years. The PWR was extended by 12 months (until September 30, 2010) to allow consideration of Week 96 data from Trial 0352.

On April 29, 2010, a Type B, pre-NDA meeting was held regarding the sponsor's planned September 2010 filing of a pediatric NDA for Viread oral powder for HIV-1 infection. A 48-week interim clinical study report (CSR) for Trial 0352 was submitted on October 22, 2009 with earlier PK and safety trials that used the 75 mg-strength tablet and oral suspension (Trials 926, 927, and 983). Conclusions drawn included the fact that exposures following the 75-mg tablet were not significantly different from adult exposures resulting from the 300 mg daily dose, and that the 8 mg/kg dose for pediatric patients was reasonable to consider in order to achieve effective adult exposures based on these PK studies. DAVP was concerned that an age-appropriate formulation had not been developed for all age groups in Trial 0352. Subjects were thought to have possibly had suboptimal exposures to the drug because of large volumes of powder required. Smaller or scored tablets were recommended for those who could swallow them (ages 6 years and older). The sponsor was encouraged to consider developing a reduced-strength tablet, and to revise the PWR accordingly.

On July 14, 2010, the sponsor proposed introduction of three reduced-strength tablets – 150 mg, 200 mg, and 250 mg – for use in patients weighing 17 to < 35 kg and who were able to swallow tablets. (b) (4) . The sponsor planned to submit an sNDA to introduce tablets without *in vivo* BE study.

On July 16, 2011, NDA 22577 and sNDA 21-356/S-038, containing data on Viread oral powder and Viread reduced strength tablets, respectively, were submitted to the Agency for review.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant submitted the NDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate. A consult request was made to the Office of Scientific Investigations (OSI) for inspection of both the Clinical sites at (b) (4) . The inspection was also to include the Bioanalytical site at Gilead Sciences, Inc., Durham, NC. The inspections were to be conducted in order to assess significant clinical and pharmacokinetic results pertinent to the decision on whether or not to grant approval.

3.2 Compliance with Good Clinical Practices

According to the applicant, Trial GS-US-104-0352 was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

3.3 Financial Disclosures

The sponsor submitted financial information pertinent to the application. The sponsor and all the principal investigators and sub-investigators for Trials GS-US-104-0352 and GS-US-104-0312 certified that they did not hold any financial interest or arrangements as per 21 CFR Part 54(a)(3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Viread is an FDA-approved drug in its 300 mg tablet form. Please see CMC review by Dr. Rao Kambhampati for further details.

CMC reviewed the new oral powder formulation, as well as the formulation and dissolution properties of the reduced-strength tablets in order to assure that the tablets were the same formulation as the marketed 300 mg Viread tablet.

Briefly, Viread oral powder (40 mg/gram of powder) contains tenofovir disoproxil fumarate as the Active Pharmaceutical Ingredient (API). The API was previously approved for use in a single ingredient drug product (Viread tablets) and in fixed dose combination tablets (Truvada Tablets, Atripla Tablets, and Complera Tablets).

Viread oral powder consists of a white, taste-masked, microencapsulated granules containing 40 mg of tenofovir DF per gram of powder. Sixty grams of TDF oral powder is packaged in (b) (4) mL sized white HDPE bottles. A dosing scoop is packaged with each bottle. The scoop delivers one gram of the oral powder. Each bottle contains (b) (4) g of TDF, which is equivalent to (b) (4) g of TDF (free base) as active ingredient, with excipients.

Tenofovir DF is manufactured by first performing a (b) (4)

The CMC review team has concluded that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. They recommend approval pending completion of satisfactory manufacturing inspections, which were outstanding at the time of this review.

4.2 Clinical Microbiology

Please see Microbiology review by Dr. Narayana Battula for further details. The pharmacologic and virologic activity of TFV/TDF was evaluated and provided in the original NDA (21-356). A virology genotyping substudy was conducted on all subjects who discontinued the trial due to virologic failure, or who had HIV RNA ≥ 400 copies/mL at Weeks 48, 96, and 144, or upon early discontinuation (prior to January 14, 2010 cutoff date). Nineteen of the 89 subjects who received TDF in the trial (21%) qualified for the substudy, and data on baseline HIV-1 genotyping from 17 of these 19 subjects were available. Five of the 17 (29%) were randomized to d4T/ZDV, and the remainder to TDF.

The most common nucleoside reverse transcriptase inhibitor (NRTI) resistance-associated substitution was M184V (12 subjects, or 71%), followed by thymidine analog-associated mutations (TAMs) (4 subjects, or 24%), including M41L, L210L/W, T215C/Y, D67D/N, K70K/R, T215T/I, and K219K/E/Q (among others). All subjects with TAMs also had M184V. All failures had past experience with d4T or ZDV, which could select for TAMs, while experience with lamivudine (3TC) or emtricitabine (FTC) could select for M184V/I.

One subject (3106-9093) in the TDF group had two substitutions, K65R and Y181C, and experienced an early increase in HIV viral load before discontinuing the trial after Week 4. The HIV-1 reverse transcriptase (RT) substitutions K65R and Y181C were detected in the Week 4 plasma sample for this 3 year old subject. The pattern of resistance was consistent with the use of TDF and the concomitant antiretroviral drugs that the subject had previously taken (subject was on a 4-drug HAART regimen prior to switching to TDF: ZDV + abacavir (ABC) + 3TC + nevirapine (NVP)). The rapid detection of resistance substitutions suggests preexisting resistance at trial entry, though development of resistance after switching to TDF is also possible. No other subject analyzed in the trial had HIV-1 with K65R, the TDF-associated substitution.

4.3 Preclinical Pharmacology/Toxicology

Viread is an FDA-approved drug, and no new toxicology data were submitted, and Pharmacology/Toxicology did not, therefore, review this submission. Please refer to the original NDA review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tenofovir DF is converted to TFV by serum esterases. Intracellularly, TFV is then converted through two phosphorylation reactions to its active phosphorylated anabolite, tenofovir diphosphate (PMPApp). Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate - dATP) and after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is only a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

4.4.2 Pharmacodynamics

Please see Biopharmaceutics review by Dr. Arzu Selen. Briefly, the specific key product attributes or characteristics that were critical for the intended in vivo performance included: the formulation studied and the final proposed product is the same; the findings from the relative bioavailability trial (GS-US-104-0312) that showed that the Viread oral powder and the 300 mg tablet had comparable AUC; taste-masking (micro-encapsulated granules, with (b) (4)); the fact that the vehicles used for administration of the oral powder were suitable

for dosing (applesauce, yogurt, baby food, and pudding, with applesauce and yogurt being the best due to the media pH being around 4). The powder must be administered immediately after mixing with the vehicle.

Table 4 shows a comparison of the oral powder and tablets in terms of dissolution.

Table 4. Summary of Dissolution Profiles for Tenofovir DF

Time (min)	300-mg Tablet (Lot 08VR002R)*	250-mg Tablet (Lot J1010F)	200-mg Tablet (Lot J1010D)	150-mg Tablet (Lot J1010B)	Oral Powder (Lot AD0602C1)
10					
20					
30					
45					

(b) (4)

Source: Dr. Arzu Selen
*Mean of 12 dosage units
**The first time point during dissolution of the oral powder was 15 minutes, at which time tenofovir DF was 81% dissolved

Each of the proposed reduced-strength tablets is proportionally equivalent in composition to the approved 300 mg strength tablets, and bioequivalence trials were therefore not conducted for the 150 mg, 200 mg and 250 mg tablet strengths.

4.4.3 Pharmacokinetics

Please see Clinical Pharmacology review by Dr. Dionna Green for further details.

Trial GS-US-104-0352 is a Phase III, randomized, open-label trial that evaluated the safety and efficacy of switching d4T or ZDV to TDF versus continuing d4T or ZDV in 97 HIV-infected, virologically-suppressed subjects taking HAART. The randomized phase continued for 48 weeks, and this was followed by a 96-week extension period (Weeks 48 to 144) during which eligible subjects who completed this randomized period were given the option to either continue or initiate TDF (All TDF phase). The pharmacokinetics of TDF were evaluated in a subset of 23 HIV-1 infected subjects in the trial who were receiving the oral powder. Tenofovir DF was administered as either the approved adult tablet or as the oral powder.

The applicant's proposed dose for Viread oral powder was 8 mg/kg per day, and the rationale for this dose was based on the results from two previously conducted pilot trials. Trial GS-01-926 was a Phase I, open-label, 96-week single-dose and multiple-dose PK, safety and virologic response trial that enrolled 18 subjects ranging in age from 6 to 16 years, nine of whom were between 6 and < 12 years of age. The single dose of TDF in these nine subjects produced an $AUC_{0-\infty\ tau}$ of 2610.29 ng.hr/mL (SD 27.89) on Day 1, while multiple-dose of TDF produced in eight subjects, an $AUC_{0-\infty\ tau}$ of 3628.95 ng.hr/mL (SD 33.44) at Week 4. The range of AUCs from historical adult data at steady-state is 2742 to 3297 ng.hr/mL, so the results from the pediatric data, though just out of this range, do not appear to be extremely divergent.

Trial GS-01-927 was a Phase I/II, open-label, 96-week single-dose and multiple-dose dose-finding PK and safety trial that enrolled 7 subjects ranging in age from 9 to 16 years (four subjects were between 9 and < 12 years of age). The single dose of TDF in two of these subjects produced an $AUC_{0-\infty\ tau}$ of 1239.12 ng.hr/mL (SD 0.87) on Day 1, while multiple-dose of TDF in two subjects produced an $AUC_{0-\infty\ tau}$ of 3687.63 ng.hr/mL (SD 55.71) at Day 7. As noted, the range of AUCs at steady-state from historical adult data is 2742 to 3297 ng.hr/mL, so these results, as with those from Trial 926, do not appear to be significantly out of this range.

The PK results from both trials 926 and 927 suggested that a dose of 8 mg/kg per day of Viread oral powder in children < 12 years of age appeared to approximate effective adult exposures and FDA reviewers agreed with this dose for the Phase 3 trial.

In Trial 0352, the question of whether drug exposures in subjects 2 to < 12 years of age were significantly different from effective adult exposures, was considered by Clinical Pharmacology. It was determined that exposures in children less than 12 years of age were slightly lower than adult exposures. Table 5 shows a summary of steady-state AUC_{tau} for TDF by age group, after the results from a single 9 year-old subject (PID 9050) was removed as the AUC_{tau} was out of range at 960 ng.hr/mL.

Table 5. Steady State AUC_{tau} at Four Weeks for Tenofovir DF by Age Group

TDF Plasma PK Parameter (Units)	**Tenofovir DF 8 mg/kg**		
	Overall N=22	**2 to < 6 years N=12**	**6 to < 12 years N=11**
AUC_{tau} (ng.hr/mL) Mean (% CV)	2661.97 (38.2)	2679.1 (39.9)	2641.41 (38.2)

The steady-state AUC_{tau} for tenofovir DF from historical adult data was determined from previously completed trials, and showed that at the 28^{th} dose (~Week 4), AUC_{tau} was 3020 ng.hr/mL. After excluding the single low outlier, the mean difference in AUC_{tau} between adults and pediatric subjects was approximately 11.2% for subjects 2 to < 6 years of age, and 12.5% for subjects 6 to < 12 years of age. The mean differences in the pediatric AUC_{tau} in both age groups were not great, and one may conclude, therefore, that the exposure in pediatric subjects approximated that in adult subjects.

The effect of food on the PK of TDF has been explored. Administration of the drug following a high-fat meal has been shown to increase the drug's bioavailability, to increase AUC by 40%, and to increase C_{max} by 14 percent. All PK trials in adults and pediatric subjects involved the administration of TDF following a meal on the PK sampling days. Trials GS-01-392 and GS-00-909 produced data on administration with food (efficacy supplement 2002), specifically under fasted conditions and with a light meal, respectively. Administration of TDF with a light meal

did not have any significant effect on TDF PK compared with administration under fasted conditions.

5 Sources of Clinical Data

This submission contains data from a Phase III randomized, open-label trial that was conducted in pediatric subjects in 9 trial sites (six in the US, one in Panama, and one in the United Kingdom). Electronic materials submitted included the GS-US-104-0352 data for Weeks 0 to 48, and Weeks 48 to 144. Datasets for the trial were submitted as SAS transport files, and comprised demographic, safety and efficacy data. Case Report Forms (CRFs) for all subjects who died, for all subjects who withdrew from the trial due to related or unrelated adverse events, and for all subjects who experienced serious adverse events (SAEs) during trial drug dosing were included. In addition, narratives were provided for all subjects who experienced deaths, SAEs (drug-related and non drug-related), and all drug-related AEs leading to withdrawal.

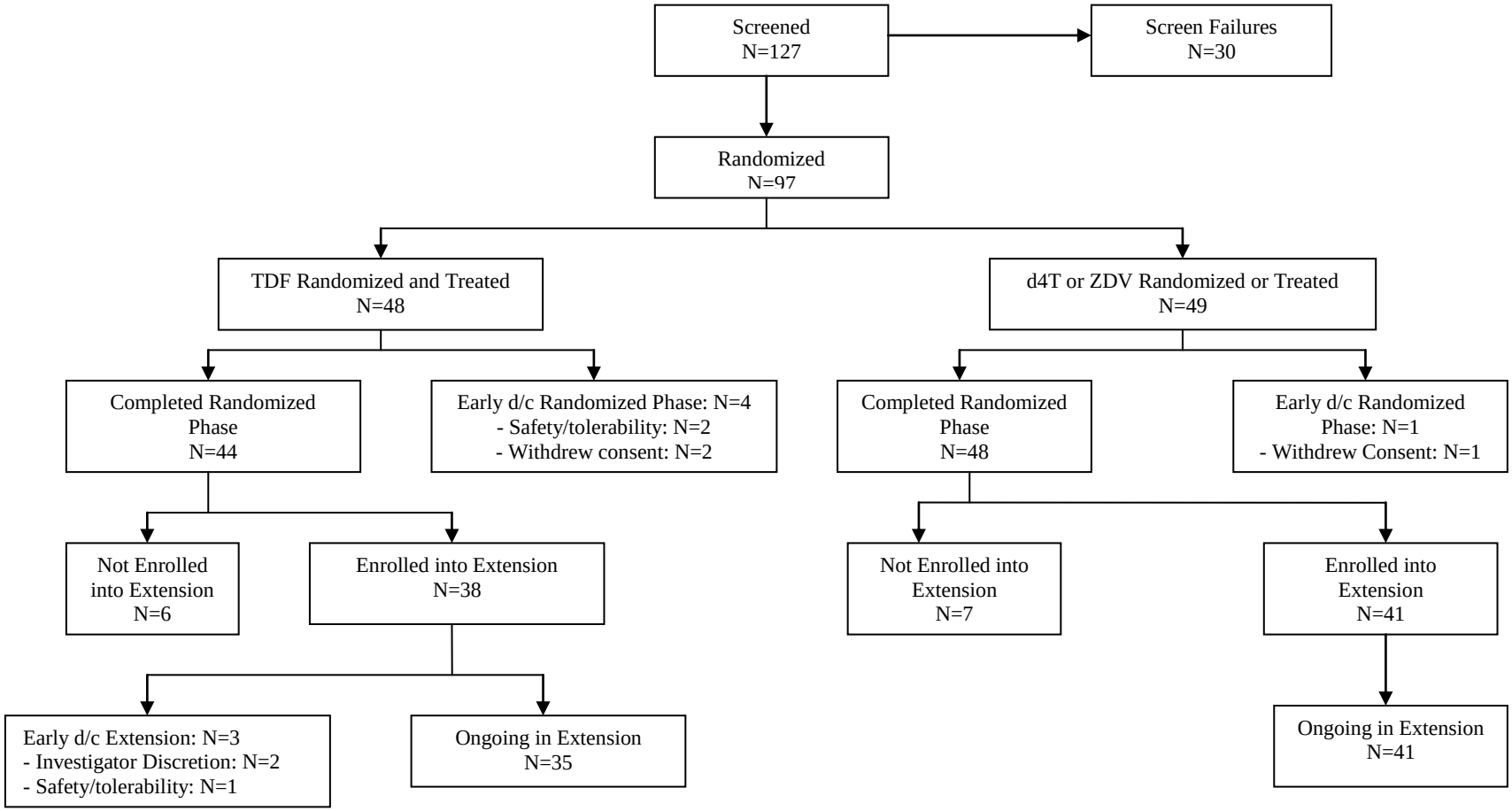
5.1 Tables of Studies/Clinical Trials

Table 6 summarizes the subject disposition of the clinical trials that were included in the submission. Figure 1 shows the disposition of subjects enrolled in clinical Trial 0352 to Week 48.

Table 6. Clinical Trial Submitted in Support of NDA Application

Trial Name	Type of Trial	Number of Subjects Enrolled	Number of Subjects with ≥ 48 week data (ITT)	Number of Subjects with ≥ 96 week data (All TDF)
GS-US-104-0352	Phase III randomized, open-label pediatric trial	97	92	89
GS-US-104-0312	Phase I two-way crossover, randomized bioavailability/bioequivalence trial	32 (Evaluable: 30)	Not applicable	Not applicable

Figure 1. Disposition of Enrolled Population (Week 48 Status), Trial 0352



5.2 Review Strategy

The clinical information provided by the applicant for this trial was reviewed for efficacy, safety, and tolerability. The conclusions drawn by the applicant were independently corroborated through analyses conducted by the FDA. The primary endpoint and secondary endpoints in the trial were confirmed by this reviewer, who also evaluated trial design, subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results using JMP Statistical software.

Similar to other pediatric trials which evaluate safety and effectiveness of ARVs, this trial was relatively small and not powered for optimal statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe the findings.

Note that for all tables and figures that were not created by this reviewer, a footnote has been included to describe the source of the data. If the table or figure is created by this reviewer, no footnote is included.

5.3 Discussion of Individual Studies/Clinical Trials

GS-US-104-0352 was the pivotal trial evaluating the use of tenofovir disoproxil fumarate (both the marketed adult tablet and the new oral powder) in pediatric subjects. The trial was submitted in support of the approval of TDF for treatment of HIV-1 in pediatric subjects 2 to < 12 years of age in combination with other antiretroviral agents. The reduced-strength tablets (150 mg, 200 mg and 250 mg) were not studied in this trial.

GS-US-104-0352 is a Phase III randomized, open-label trial in pediatric subjects 2 to < 12 years of age with documented HIV-1 infection who were virologically suppressed (plasma HIV-1 RNA < 400 copies/mL) at baseline on their d4T- or ZDV-containing highly active antiretroviral therapy (HAART) regimen. Safety, tolerability, PK parameters and efficacy of TDF in combination with other antiretroviral agents were evaluated.

The trial was divided into two stages. The initial 48 weeks of the trial consisted of a randomized, open-label, parallel-group treatment period. Eligible subjects were randomized in a 1:1 ratio to either replace d4T or ZDV with TDF (Treatment Group A) or to continue d4T or ZDV (Treatment Group B) in their existing HAART regimen for 48 weeks. Randomization was stratified by whether a subject was currently on d4T or ZDV. The primary therapy period lasted from December 28, 2006 to April 6, 2009.

Subjects who completed 48 weeks of randomized treatment who continued to be less than 18 years of age were given the option to either continue or initiate TDF in the first of two 96-week trial extensions (collectively referred to as the extension phase). Switching to TDF from d4T or ZDV could only be done if the investigator deemed the switch safe and beneficial for the subject. After completion of the first 96-week trial extension, currently enrolled subjects who were

benefitting from TDF and remained < 18 years of age were given the option to continue to receive TDF for an additional 96 weeks, or until TDF becomes commercially available in the country of enrollment.

The primary objective of the trial was to assess the efficacy of switching to TDF compared to continuing d4T or ZDV in maintaining virologic suppression (plasma HIV-1 RNA < 400 copies/mL) in HIV-1 infected children at Week 48. Secondary objectives included the following: to evaluate the safety and tolerability of TDF in HIV-1 infected children; to evaluate the effects of switching from d4T or ZDV to TDF, versus continuing d4T or ZDV on bone mineral density (BMD), fasting lipid parameters, and fat distribution; and to evaluate the PK of TDF in a subset of HIV-1 infected children receiving TDF oral powder.

Efficacy was assessed through plasma HIV-1 RNA levels and CD4 cell counts and percentages at each trial visit. Subjects who switched at Week 48 from d4T or ZDV to TDF, were required to undergo additional trial assessments at Week 52 following the switch in therapy.

Tenofovir steady-state pharmacokinetic parameters were assessed in the trial for a subset of subjects following at least 4 weeks of dosing with TDF oral powder. These parameters included: C_{max}, C_{max}, $C_{max/dose}$, T_{max}, C_{last}, T_{last}, C_{tau}, .λz (Kel), $T_{½}$, AUC_{tau}, AUC_{tau}/dose; $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}$/dose, and CL/F. Pharmacokinetic sampling occurred over a period of 12 hours, and specimens were drawn at 0, 1, 2, 4, 8, and 12 hours after tenofovir DF dosing.

Safety was monitored through physical examinations (complete or symptom-directed) and serial laboratory testing (chemistry, hematology, and urinalysis) at each trial visit. Bone biochemical marker assessments were made at baseline, Weeks 4, 16, 24, 48, and at 48-week intervals during the extension phase. In addition, dual-energy x-ray absorptiometry (DEXA) scans of the lumbar spine and whole body were conducted at baseline, Weeks 24 and 48, and at 24-week intervals during the extension phase to measure spine BMD, total body BMD, fat distribution, and body morphology.

Information was collected and assessed regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving TDF, particularly from those who experienced loss of virologic response. A virologic substudy is being conducted on HIV-1 from all subjects in either treatment group who discontinued the trial due to virologic failure (defined as two consecutive measurements of plasma HIV-1 RNA > 1000 copies/mL that could not be attributed to nonadherence) or who had HIV-1 viral load ≥ 400 copies/mL at Week 48, Week 96, or at early discontinuation.

6 Review of Efficacy

Efficacy Summary

GS-US-104-0352 was a randomized, open-label trial in which HIV-infected pediatric subjects 2 to < 12 years of age who were receiving d4T or ZDV as part of a HAART regimen, who either switched from d4T or ZDV to TDF, or continued d4T or ZDV in their existing HAART regimen, for 48 weeks. Following completion of 48 weeks of randomized treatment, those subjects who continued to be less than 18 years of age were given the option to either continue or initiate TDF in the first of two 96-week trial extensions.

Tenofovir DF adult tablets and oral powder, in combination with other antiretroviral agents, demonstrated good antiviral activity over the 48 week trial period. Overall, 42/48 (87.5%) of trial subjects in the TDF group, and 43/49 (87.8%) of subjects in the d4T or ZDV group achieved an HIV RNA level < 400 copies/mL by Week 48, using the snapshot approach at calculating virologic response. The difference between the results in the treatment groups was -0.3%, 95% CI -13.4% to 12.9%; the lower bound of this CI was greater than -15%, so the noninferiority criteria of TDF were met. The virologic response in this pediatric population was greater than one would expect in a treatment-experienced adult population using TDF.

In Trial GS-US-104-0352, there did not appear to be any significant difference in efficacy based on subgroup classifications such as age, gender, race, and CD4 percentage. The virologic response was durable to Week 48.

6.1 Indication

The proposed indication under evaluation is tenofovir disoproxil fumarate for use in the treatment of HIV-1 infection for pediatric patients 2 to < 12 years of age for 48 weeks.

6.1.1 Methods

The primary efficacy endpoint of the trial was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48, as compared between the two treatment groups in the randomized period.

The secondary efficacy endpoints included the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, and the change from baseline in CD4 cell count and CD4 percentage between the two treatment groups at Week 48.

At the time that DAVP deemed Trial Protocol GS-US-104-0352 safe to proceed, the primary analysis accepted by the Agency for HIV trials was Time to Loss of Virologic Response (TLOVR). Since that time, the Agency had transitioned to use of the "snapshot" approach, which is an efficacy analysis approach adopted in order to produce results for virologic response that

utilize only HIV RNA data at the visit of interest. Applicants are requested to conduct their primary analysis in HIV treatment trials using the snapshot analysis. The applicant presented results from both TLOVR and the snapshot approach in the clinical study report.

Medical Officer comment: According to the applicant, for efficacy analyses assessing the endpoints HIV-1 RNA concentrations < 400 copies/mL or < 50 copies/mL, missing data were handled using the missing = failure (M = F) method, which included the subject in the denominator but not in the numerator when calculating the percentage of subjects who met the endpoint criteria. Changes from baseline in CD4 cell count and percentage were analyzed using the missing = excluded (M = E) method, which only included reported data in calculations.

In addition to virologic parameters, immunologic parameters (CD4 cell count and percent) were also assessed as part of the efficacy evaluation.

6.1.2 Demographics

The main demographic characteristics of the trial population are shown in Table 7. The mean age was 7 years (range, 2 to 15 years), and this was the same in both treatment groups. Of the total 97 subjects enrolled, 5 subjects were included who were ≥ 12 years and were < 18 years at enrollment, leaving a total of 92 subjects who fulfilled the prespecified enrollment criteria. Only the 92 subjects who were eligible and correctly enrolled were included in efficacy calculations.

The gender distribution was fairly well-balanced, with 52% male and 48% female subjects. The majority of enrolled subjects were classified racially as "Other" (68%), and 65 /66 (98%) of these were "mestizo," or a mixture of Black, continental Spanish, and indigenous ethnicities. This racial distribution is not unexpected, as most of these pediatric subjects were enrolled from Panama (72/97, or 74%).

Table 7. Subject Demographics by Treatment Group, Weeks 0 to 48

Characteristics	**TDF** **N=48** **n (%)**	**d4T or ZDV** **N=49** **n (%)**	**Total** **N=97** **n (%)**
Age (years)			
Mean (SD)	7 (3.3)	7 (2.6)	7 (3)
Range	2-15	2-14	2-15
Sex (n, %)			
Male	21 (44)	29 (59)	50 (52)
Female	27 (56)	20 (41)	47 (48)
Enrollment by Country			
Panama	33	39	72
United States	13	9	22

Characteristics	TDF N=48 n (%)	d4T or ZDV N=49 n (%)	Total N=97 n (%)
United Kingdom	2	1	3
Race (n, %)			
American Indian/Alaska Native	2 (4)	0	2 (2)
Asian	1 (2)	0	1 (1)
Black	13 (27)	6 (12)	19 (20)
White	3 (6)	6 (12)	9 (9)
Other	29 (61)	37 (76)	66 (68)
Mestizo	28	37	65
Native Indian (Kuna)	1	0	1

SD – Standard deviation

Table 8 shows the baseline characteristics of enrolled subjects. The mean weight was 25 kg (range, 10.1 to 63.3). This weight approximated the 50th percentile weight of the majority of American children at the age of 7 years (based on growth charts from the National Center for Health Statistics), and although most enrolled subjects were from outside the United States, the comparison suggests that malnutrition or other factors that might cause weight to be lower, were not pertinent in this subject population. The mean height was 119 cm (range, 78 to 155), and this, also, is the mean height for the majority of American children at the mean age of subjects in this trial.

Table 8. Subject Baseline Characteristics by Treatment Group, Weeks 0 to 48

Characteristics	TDF N=48 n (%)	d4T or ZDV N=49 n (%)	Total N=97 n (%)
Weight (kg)			
Mean (SD)	26 (12)	24 (7.7)	25 (10.1)
Range	10.1-63.3	10.2-45	10.1-63.3
Height (cm)			
Mean (SD)	118 (19.8)	119 (16.7)	119 (18.2)
Range	78-155	82-152	78-155

Baseline HIV Characteristics

The median CD4 count was 1095 overall, and the median CD4 percentage was 34%. This suggests that the enrolled subjects were not significantly immunosuppressed. A total of 77/97 subjects (79%) had plasma HIV-1 RNA < 50 copies/mL at baseline, followed by 17/97 subjects (18%) with baseline HIV-1 RNA 50 to < 400 copies/mL. The enrolment criteria for these subjects specified that they had to be virologically suppressed at trial entry, and all were on a suppressive HAART regimen at baseline.

Table 9. Subject Baseline Disease Characteristics by Treatment Group, To Week 48

Characteristics	**TDF N=48 n (%)**	**d4T or ZDV N=49 n (%)**	**Total N=97 n (%)**
CD4 Cell Count (per mm3)			
Mean	1190 (541.7)	1144 (388.4)	1167 (468.6)
Median	1061	1149	1095
N	48	49	97
Range	500-3671	407-2313	407-3671
CD4 Percentage (%)			
Mean	34 (7.4)	33 (6.8)	36 (7.1)
Median	34	33	34
N	48	49	97
Range	18-48	17-51	17-51
Plasma HIV-1 RNA (copies/mL)			
< 50	36 (75%)	41 (84%)	77 (79%)
50 to < 400	11 (23%)	6 (12%)	17 (18%)
400 to < 1000	1 (2%)	1 (2%)	2 (2%)
≥ 1000	0	1 (2%)	1 (1%)

The applicant did not provide information on Phenotypic Sensitivity Score (PSS) or Genotypic Sensitivity Score (GSS), or previous antiretroviral drug use as a measure of extent of treatment experience or resistance.

6.1.3 Subject Disposition

A total of 127 subjects were screened, and of the 97 randomized and treated subjects, 92 completed 48-week randomized treatment period (44 subjects (92%) in TDF group and 48 subjects (98%) in d4T or ZDV group).

Two subjects in the TDF group were discontinued due to safety, tolerability or efficacy reasons. Subject 3106-9092 was discontinued on Day 13 because the child's parent stopped trying to dose the subject. Subject 3106-9093 discontinued TDF on Day 42 due to an increase in viral load; HIV-1 RNA was > 400 copies/mL at Week 4 (Day 26) and upon retesting on Day 35 (see Section 4.2). No subjects in the d4T or ZDV group were discontinued due to safety, tolerability or efficacy reasons.

Three subjects were discontinued due to withdrawal of consent. Subject 2880-9075 discontinued on Day 260 because the subject was unable to comply with trial visits (switched to commercial TDF). Subject 1800-9079 discontinued TDF on Day 293 as they did not like taking the TDF oral powder. Subject 2767-9068 discontinued the d4T or ZDV group on Day 16 because they did not want to undergo DEXA evaluations.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis endpoint of the trial was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48, as compared between the two treatment groups in the randomized period.

Results

The FDA's snapshot algorithm was used to calculate the primary endpoint i.e. defined as the proportion of subjects achieving HIV RNA < 400 copies/mL. The results are shown in Table 10 and were corroborated by this reviewer and by Dr. Wen Zeng of the Statistics Team. It should be noted again that a total of 92 subjects (44 in the TDF group, 48 in the d4T or ZDV group) were eligible and correctly enrolled in the randomized treatment phase of the trial. The efficacy calculations were completed using the data from these 92 subjects; five additional subjects over the age of 12 years were incorrectly enrolled and randomized (TDF N=4, original regimen N=1) but are not included in the efficacy analysis.

Table 10. Virologic Outcome at Week 48 (HIV-1 RNA < 400 copies/mL): Snapshot Analysis*

	TDF N=44	**d4T or ZDV N=48**	**Difference (95% CI)**
Virologic Success at Week 48; n, (%)	39 (88.6%)	43 (89.6%)	-0.9% (-13.7% to 11.8%)
Virologic Failures; n, (%)	5 (10.4%)	5 (10.2%)	
Ongoing and viral load > 400 copies/mL	4 (8%)	4 (8%)	
Switch in background regimen not allowed by protocol	1 (2.1%)	1 (2.1%)	
No Virologic Data at 48 Week Window			
Discontinued trial/trial drug due to AE or death	0	0	
Discontinued trial/trial drug for Other Reasons	1 (2.1%)	1 (2.0%)	
Missing data during window but on study	0	0	

*Source: Efficacy results from Dr. Wen Zeng, Statistics Reviewer. Disposition data from submission.

At Week 48, 39/44 subjects (89%) in the TDF group and 43/48 subjects (90%) in the d4T or ZDV group had virologic success, with HIV-1 RNA < 400 copies/mL. The difference in the percentage of subjects with virologic success was -0.9% and the 95% confidence interval (CI) was -13.7% to 11.8%. Given the fact that the lower bound of the CI for the difference was greater than -15%, TDF met the criteria for treatment noninferiority, using the snapshot analysis.

One subject in the TDF group discontinued the trial prematurely because of virologic failure/lack of efficacy, and 3 subjects (2 subjects in the TDF group and 1 subject in the d4T or ZDV group)

discontinued for other reasons. Two subjects added new antiretroviral drug to their regimen during the randomization period (Subjects 9044 from the TDF group, and Subject 9054 from the d4T or ZDV group). These two subjects were not counted as failures by the applicant but are considered so in the FDA analysis.

The applicant did not meet the pre-specified primary efficacy endpoint using the older analysis approach.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints included the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, and the change from baseline in CD4 cell count and CD4 percentage between the two treatment groups at Week 48.

Virologic parameters at Week 48 determined by the applicant were similar to those found by this reviewer. Using the snapshot approach, a total of 36/48 (75.0%) of subjects in the TDF group and 39/49 subjects (79.6%) in the d4T or ZDV group had HIV-1 RNA < 50 copies/mL. The difference in the percentage of subjects was -4.6%, and the 95% CI was -21.2% to 12.1%. The criteria for noninferiority were not met using this analysis.

Changes in CD4 percentage were minimal, given the fact that subjects were virologically suppressed at baseline and had relatively normal CD4 counts and percentage at study entry.

6.1.6 Other Endpoints

Safety and efficacy of TDF use in pediatric subjects at Week 96) (after all continuing subjects received TDF from Weeks 48 to 96) was assessed, but because this "All TDF" group was non-randomized and essentially uniform in their use of TDF, any comparison between the TDF and original d4T or ZDV groups should be assessed with caution. That said, similar proportions of subjects had HIV-1 RNA < 400 copies/mL at Week 96 in the All TDF group, using the M=E approach (89%) and M=F approach (86%). No clinically significant differences were noted between the TDF and original (d4T or ZDV)/TDF groups.

Resistance Development

See Section 4.2 and Dr. Narayana Battula's Virology review for details.

The virology genotyping substudy was conducted on HIV-1 isolates from all subjects who discontinued due to virologic failure or who had HIV-1 viral load ≥ 400 copies/mL at Week 48, Week 96, Week 144, or upon early discontinuation prior to the data cutoff date for the Week 96 analysis. Due to the low HIV-1 viral load at trial entry, baseline genotyping was not conducted. A total of 19 subjects were enrolled in the substudy based on Week 48 virologic data.

At baseline, 17 of these subjects had banked plasma samples tested (12 in TDF group, 5 in d4T or ZDV group). Three subjects (Subjects 1578-9010, 1578-9019, and 1578-9050) had the M184V mutation in their HIV-1 isolate, either alone or with other RT or major PI-associated mutations. Subject 1578-9019 had multiple TAMs that were suggestive of previous ZDV use. Subjects 1578-9019 and 1578-9050 had major protease mutations that were consistent with current or past use of a PI. Subject 1578-9033 did not have mutations associated with drug resistance in her HIV-1 isolate.

6.1.7 Subpopulations

Analysis by Age

The efficacy of TDF was analyzed by age (Table 11): 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years. Age did not have a significant effect on the efficacy of TDF, which was fairly high across age groups. In the 6 to < 12 years age group, the efficacy in the TDF group was 82% compared with 94% in the d4T or ZDV group, but it is unclear why this slight difference was seen. The difference is also seen in the 12 to < 18 years age group, though the small numbers in the group make it difficult to draw any conclusions.

Medical Officer comments: In the context of larger adult clinical trials, the efficacy was somewhere between that of treatment-naïve and treatment-experienced subjects. The trial involving treatment-experienced adult subjects (Study 907) did not compare directly d4T or ZDV with TDF, and the pediatric subjects in Trial 0352 were already successful on their regimens at baseline (rather than previous treatment failures at baseline). The trials involving treatment-naïve subjects did include d4T or ZDV as comparators (Study 934 used ZDV, Study 903 used d4T), but conclusions made on efficacy are difficult given the subjects' lack of treatment experience at baseline, the composition of the background regimens, and the divergent efficacy results with each of the two drugs: In Study 903, virologic response at Week 48 was higher at 82% in the d4T group compared to 79% in the Viread group, while in Study 934, virologic response at Week 48 was lower in the ZDV group compared at 73% compared with 84% in the Viread group.

Table 11. Efficacy at Week 48, Stratified by Age

Subjects with Plasma HIV-1 RNA < 400 copies/mL; n/N (%)	**2 to < 6 years**		**6 to < 12 years**		**12 to < 18 years**	
	TDF N=16	**d4T or ZDV N=14**	**TDF N=28**	**d4T or ZDV N=34**	**TDF N=4**	**d4T or ZDV N=1**
Baseline	16 (100%)	14 (100%)	27 (96%)	32 (94%)	4 (100%)	1 (100%)
Week 48	14 (88%)	12 (86%)	23 (82%)	32 (94%)	3 (75%)	1 (100%)

Analysis by Gender

The efficacy of TDF was analyzed by gender (Table 12). There were some slight differences in the efficacy findings in males compared with females, but the reason for the differences is unclear, as there are no data to support the notion that TDF works differently in males and females (pediatric or adult). Of note, the efficacy in males on TDF at Week 48 was higher at 95%, compared with 74% in females, while the efficacy was lower in males on d4T or ZDV at Week 48, at 86%, compared with females at 95%. There is no consistent trend to the differences, and it is likely that they occurred by chance. A larger sample size might have produced more consistency in the findings.

Table 12. Efficacy at Week 48, Stratified by Gender

Subjects with Plasma HIV-1 RNA < 400 copies/mL; n/N (%)	**Male**		**Female**	
	TDF N=21	**d4T or ZDV N=29**	**TDF N=27**	**d4T or ZDV N=20**
Baseline	20 (95%)	28 (97%)	27 (100%)	19 (95%)
Week 48	20 (95%)	25 (86%)	20 (74%)	19 (95%)

Analysis by Race

The efficacy of TDF was analyzed by race (Table 13). For ease of comparison, the applicant combined the "Other" category with the "Whites" (all of the subjects in the "Other" category except one, was mestizo). The efficacy at Week 48 appears to have been higher in whites, in both the TDF and d4T or ZDV groups. There are no data to suggest that race or ethnicity plays a role in how TDF works in the body, either in adults or children. The number of black subjects is low compared with the whites, and one might surmise that a larger sample size would have allowed for a more interpretable comparison between the races enrolled. Despite these results, there is little reason to believe that TDF will lead to differing efficacy depending on race.

Table 13. Efficacy at Week 48, Stratified by Race

Subjects with Plasma HIV-1 RNA < 400 copies/mL; n/N (%)	**Black**		**White***	
	TDF N=13	**d4T or ZDV N=6**	**TDF N=31**	**d4T or ZDV N=43**
Baseline	12 (92%)	6 (100%)	31 (100%)	41 (95%)
Week 48	10 (77%)	5 (83%)	27 (87%)	39 (91%)

*White: Includes Whites and Other (mestizo) categories, minus the single Native Indian subject

Analysis by CD4 Percentage

The efficacy was analyzed by CD4 percentage (Table 14). Though the number of subjects with CD4 percentage < 25% was small, a significant difference was noted at Week 48 between the two CD4 percentage categories (< 25% and ≥ 25%). For the TDF group, virologic response was greater in subjects who had CD4 percentage ≥ 25% (86% compared with 60% in subjects with CD4 percentage < 25%). The trend was reversed for subjects in the d4T or ZDV group; efficacy was higher in the CD4 percentage < 25% category (100%), compared with the CD4 percentage ≥

25% category (88%). To reiterate, comparison between the groups is difficult, given the smaller number in the lower CD4 percentage category, but based on the TDF findings, it appears that subjects with less immunologic suppression had a higher virologic response compared with those with more immunologic suppression.

Table 14. Efficacy at Week 48, Stratified by CD4 Percentage

Subjects with Plasma HIV-1 RNA < 400 copies/mL; n/N (%)	**CD4% < 25%**		**CD4% ≥ 25%**	
	TDF N=5	**d4T or ZDV N=6**	**TDF N=43**	**d4T or ZDV N=43**
Baseline	5 (100%)	6 (100%)	42 (98%)	41 (95%)
Week 48	2 (60%)	6 (100%)	37 (86%)	38 (88%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose selection for TDF use in pediatric subjects in this trial was based upon pharmacokinetic parameters discussed in Section 4.4.

In summary, the recommended dose for TDF for pediatric subjects is as follows:

> *Tablets*: for pediatric patients weighing ≥17 kg (≥37 lb) 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
>
> *Oral powder*: 8 mg/kg VIREAD oral powder (up to a maximum of 300 mg) once daily with food.

Dosage Forms and Strengths:
Tablets: 150, 200, 250 and 300 mg
Oral Powder: 40 mg per 1 g of oral powder

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The treatment effect was durable to at least Week 48, as determined by the available data to that time point. The virologic response as measured by HIV RNA below 400 copies/mL increased over time, as noted in evaluations conducted at Week 48 and at Week 96 (Sections 6.1.6).

6.1.10 Additional Efficacy Issues/Analyses

In most cases, pediatric efficacy is extrapolated, but in the case of Trial 0352, the trial provided comparative effectiveness with the use of pharmacokinetics. The potential effectiveness of TDF treatment was assessed by matching exposure to the exposure associated with efficacy of TDF in

adults. The extrapolation of efficacy for antiretroviral drugs like TDF is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[1] DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011, pp 1-279. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

7 Review of Safety

Safety Summary

Tenofovir DF administered with other antiretroviral drugs was, in general, safe and tolerable when used in pediatric subjects 2 to < 12 years of age. The nature of the adverse events noted in pediatric subjects in this trial was similar to that of adult patients. The frequency of serious adverse events and nonfatal adverse events was relatively low in these pediatric subjects. There were no fatalities reported in this pediatric trial. In terms of adverse events of interest, significant findings for renal events were low in frequency. Findings for bone events suggested less of an effect of TDF in the youngest subjects studied (2 to 5 years of age), but three subjects were found to have significant hypophosphatemia in addition to bone events. In general, there were no new or concerning safety signals noted in pediatric subjects with the use of tenofovir DF in Trial 0352.

7.1 Methods

Safety data for this NDA were provided by the applicant in the form of electronic datasets that contained tables of clinical adverse events. An Integrated Summary of Safety (ISS) was provided. Narrative summaries and case report forms were provided for all subjects who experienced one or more of the following: Deaths; all SAEs (drug-related and non-drug-related); and all drug-related AEs leading to withdrawal. Tabulations of AEs, SAEs, and study drug interruptions or discontinuations were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc.).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted using the data generated from Trial GS-US-104-0352. The safety profile of tenofovir DF has previously been established in adults using an adequate number of subjects to permit approval of the drug for marketing in 2001. GS-US-104-0352 was a pivotal pediatric trial that was conducted to assess the safety, efficacy, tolerability, and pharmacokinetics of switching d4T or ZDV to TDF versus continuing d4T or ZDV in virologically-suppressed HIV-infected pediatric subjects 2 to < 12 years of age. The initial treatment period was for 48 weeks, followed by two additional 96-week extension periods to evaluate the long-term efficacy, safety, and tolerability of treatment with TDF (end Week 144).

The pivotal pediatric trial provides an adequate number of subjects exposed to TDF to allow for an assessment of safety and tolerability.

7.1.2 Categorization of Adverse Events

The submitted data support the requirement of safety and tolerability of TDF. A total of 26 subjects aged 2 to 18 years were required to be evaluated for safety at the to-be-marketed dose or higher of TDF for 48 weeks, and the applicant enrolled a total of 97 subjects for the randomized treatment phase. The number of subjects exposed to TDF and the duration of exposure were adequate. Adverse events were depicted using MedDRA preferred terms. All adverse events were graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

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

Pooling of data from across studies other than GS-US-104-0352 was not conducted.

7.2 Adequacy of Safety Assessments

Viread is an approved drug for which a significant amount of safety data in adults are available from previously-reviewed treatment protocols. As such, the monitoring of clinical and laboratory safety parameters in this trial was considered adequate.

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

Duration of exposure to trial drug was calculated as the number of days between the first and last dose of trial drug divided by seven, inclusive, regardless of temporary interruptions in trial drug administration. Duration of exposure was expressed as total exposure in weeks.

The mean number of days of exposure for the group initially randomized to TDF was 48.2 weeks (range, 1.9 to 56.4 weeks), compared with 49.9 weeks (range, 2.3 to 53.1 weeks) in the group initially randomized to d4T or ZDV (
Table 15). The difference in duration of exposure between the two treatment groups was not statistically significant (p=0.25), even though the d4T or ZDV group received a mean of one week more study drug exposure.

Table 15. Extent of Trial Drug Exposure in Randomized Treatment Period

Total Exposure (weeks)	**TDF N=48**	**d4T or ZDV N=49**
Mean (SD)	48.2 (9.9)	49.9 (7.2)
Median	51.9	52.0
Range	1.9 – 56.4	2.3 – 53.1

p-value comparing treatment group differences, randomized treatment period: TDF vs. d4T or ZDV = 0.25

7.2.2 Explorations for Dose Response

There were no data from Trial 0352 on tenofovir dose-response or exposure-response. In addition, there was no formal exposure-response analysis conducted for the adult clinical development program.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed, and testing was found to be adequate. Following a screening evaluation, subjects were evaluated periodically for adverse events and laboratory parameters at baseline, Weeks 2, 4, 8, 16, 24, 36, and 48. For the initial 96-week extension period, assessments were conducted at Weeks 52, 60, 72, 84, 96, 108, 120, 132, 144, at Early Discontinuation, and at 30-day follow-up.

7.2.5 Metabolic, Clearance, and Interaction Workup

Trials studying metabolic, clearance and drug-drug interactions have previously been conducted for TDF, and were not part of this submission.

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

All known class adverse events were evaluated.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this trial in the randomized treatment period from Week 0 to Week 48, nor were there any deaths that occurred in the initial 96-week extension period (Weeks 48 to 144). The second 96-week extension period is ongoing at the time of this review.

7.3.2 Nonfatal Serious Adverse Events

The number of serious adverse events (SAEs) reported in the trial was relatively small. A total of two subjects in each treatment group experienced SAEs during the randomized treatment period (Weeks 0 to 48). Two subjects had SAEs in the SOC Infections and Infestations, while one subject each had SAEs classified under SOC Blood and Lymphatic System Disorders, and Respiratory, Thoracic and Mediastinal Disorders.

The SAEs by preferred term are shown in Table 16. SAEs reported in the TDF group included pneumonia and pharyngotonsillitis, while SAEs reported in the d4T or ZDV group included asthmatic crisis and lymphadenitis.

None of the SAEs were considered to be related to trial drug. Of the four SAEs reported, only pneumonia has been noted as a treatment-emergent AE (Grade 2-4) in ≥ 3% of any treatment group from 0 to 48 weeks, in Study 907, conducted in treatment-experienced adult subjects. Though the number is very small and it is difficult to make definitive conclusions based upon them, it is known that some infections occur more frequently in children compared with adults and children might be more prone to having symptomatic asthma and therefore asthmatic crises.

Table 16. Summary of Serious Adverse Events by Preferred Term, Randomized Treatment Period

Clinical AE Preferred Term	TDF N=48 n (%)	d4T or ZDV N=49 n (%)	Total N=97 n (%)
Asthmatic crisis	0	1 (2%)	1 (1%)
Lymphadenitis	0	1 (2%)	1 (1%)
Pneumonia	1 (2%)	0	1 (1%)
Pharyngotonsillitis	1 (2%)	0	1 (1%)

N= Number of subjects in group

Grade 3 and 4 Clinical Events

No Grade 3 or 4 clinical adverse events (AEs) were reported during the randomized treatment period.

In the All TDF group (Weeks 0 to 144), two Grade 3 or 4 clinical adverse events were reported. One subject, an 8 year old male, was enrolled initially in the TDF group and experienced a Grade 3 AE of hypophosphatemia at Week 72, with a serum phosphate level of 2.3 mg/dL. The subject had a second episode of this AE at Week 84, with a measured serum phosphate of 1.6 mg/dL. Trial drug was discontinued at Week 85, and the AE resolved one month later.

A second subject in the All TDF group, initially randomized to the d4T or ZDV group, experienced a Grade 3 appendicular plastron or mass secondary to abdominal and retroperitoneal fibrosis and adhesions at approximately Week 82. Trial drug was interrupted for gastrointestinal management of this AE, and trial drug was restarted six weeks later as the event had resolved.

Adverse Events by Relationship to Trial Drug During Randomized Treatment Period (Weeks 0 to 48)

Relationship to trial drug was determined using the following criteria: temporal relationship between onset and administration of trial drug; event could not be readily explained by subject's clinical state or concomitant therapies; some degree of certainty to be related based on known therapeutic and pharmacologic actions or AE profile; and clinical judgment. Based on these criteria, a total of six subjects (5 in the TDF group, and 1 in the d4T or ZDV group) were reported to have treatment-related AEs. In the TDF group, vomiting was reported in 3/48 subjects (6%), gastritis was reported in 1/48 subject (2%), nausea was reported in 1/48 subject (2%), and enuresis was reported in 1/48 subject (2%). In the d4T or ZDV group, maculopapular rash was reported in 1/49 subject (2%). No CRFs or narratives were available to corroborate that the treatment relationship criteria were fulfilled. Regardless, it appears that only a small number of treatment-emergent events occurred in the trial.

7.3.3 Dropouts and/or Discontinuations

There were no discontinuations that occurred due to either clinical or laboratory adverse events in the randomized trial period (Weeks 0 to 48.)

Few subjects discontinued trial drug after Week 48. During the extension phase (Weeks 48 to 144), four subjects in the All TDF group discontinued therapy due to adverse events. Three of these subjects experienced hypophosphatemia (initially randomized to receive TDF), and one experienced glycosuria (initially randomized to receive d4T or ZDV).

7.3.4 Significant Adverse Events

Adverse events of particular interest in this trial, as noted in the adult data applications for TDF included renal events and bone events. These were included in the submission to provide additional information regarding their potential occurrence in pediatric subjects receiving TDF. In comparison with the adult TDF safety profile, no new safety signals were identified in the pediatric data, which were evaluated from Week 0 to Week 48.

Renal Events

Renal impairment, including proximal renal tubular dysfunction, cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of TDF. Few renal adverse events were reported in this trial.

No graded abnormalities in serum creatinine were noted. Grade 1 hypophosphatemia was reported for two subjects in the TDF group and for one subject in the d4T/ZDV group. Grade 2 proteinuria was reported for one subject in the TDF group, and for three subjects in the d4T or ZDV group. Notably, no Grade 3 or 4 proteinuria was reported in either group. Grade 1 glycosuria was reported for one subject in the d4T or ZDV group, and no Grade 2, 3 or 4 urine glucose abnormalities were reported. No graded urine glucose abnormalities were reported in the TDF group.

Bone Events

HIV infection has been associated with reduced bone mineral density (BMD) in adults and children, compared to uninfected individuals, but the mechanism and its clinical significance are unclear. Antiviral treatment, including TDF appears to contribute to bone loss over the first 6 to 12 months of therapy, followed by a general stabilization after one to two years, or a slight improvement. These BMD reductions appear, in several animal and human studies, to be greater with regimens that include TDF. Given the fact that continuous bone growth and mineralization occurs in children until well into their late teens, there has been concern about the effects of TDF on BMD and subsequent bone growth and risk of fracture.

The bone data submitted by the applicant were reviewed in a consult completed by Steve Voss, M.D. of the Division of Reproductive and Urologic Products (DRUP). Please see the archived consult report (archived on November 29, 2011) for full details. A summary of the conclusions will be provided below. Of note, an adolescent trial, GS-US-104-0321, was conducted prior and was reviewed by Dr. Voss. This was a phase III, controlled trial involving 87 HIV-infected

adolescents aged 12 to 17 years, who were failing their current drug regimens, and were randomized to add either TDF 300 mg daily or placebo to an optimized background regimen for a total of 48 weeks (with the option to receive TDF in an open-label extension phase afterwards). Baseline bone density was found to be below that of the subjects' age- and gender-matched peers due to reasons that included HIV infection, co-morbidities, prior therapies and/or delayed growth. Also, the subjects' mean lumbar spine and total body BMD (as measured by DEXA scans) increased over 96 weeks of TDF therapy, though likely less than expected for their peer group. Linear growth was overall unaffected. Consistent with previous findings in adults, the TDF group had lesser gains in BMD at Week 48, and the TDF cohort showed increases in the circulating bone turnover markers.

In Trial 0352, HIV-infected subjects 2 to 11 years of age had baseline bone density that was significantly below that of their age-matched peer group (i.e. negative Z-scores), with the exception of the younger (2 to 5 years) children's total body BMD. TDF appeared to have effects on bone metabolism similar to its effects in adults and adolescents, with a tendency to increase bone turnover and, perhaps as a result, had a negative effect on BMD. There was no indication of any effect on bone growth. During the 48 week randomized treatment phase, total body BMD accrual was significantly less with the TDF group compared with d4T or ZDV group, and mean total body Z-scores appeared to decline with TDF treatment to a similar degree as in the adolescent trial. Growth was not impaired by TDF treatment, similar to the adolescent trial. Unlike the findings in the adolescent study, however, where TDF appeared to have a negative effect on lumbar spine BMD, 2 to 11 year old children maintained their baseline spine Z-scores over three years of TDF exposure. Although the TDF group lagged slightly behind the control group at week 48, the differences in Z-scores were not significant. Boys and girls had equally favorable lumbar spine results. The data for older children (6 to 11 years of age), however, were somewhat less favorable than those of the younger children (2 to 5 years of age).

Biochemical markers of bone turnover were measured. These included markers for bone resorption (serum N-telopeptide and serum C-telopeptide), markers for bone formation (serum osteocalcin and bone specific alkaline phosphatase), serum parathyroid hormone (PTH), and 25-hydroxy Vitamin D. The markers appeared to increase from baseline somewhat more in the TDF group than in the comparison group, and then returned to baseline after the first year, as seen in previous adult and adolescent trials. Of note, however, three subjects (9004, 9030, and 9071) with substantial bone loss during the trial also exhibited hypophosphatemia and other features suggestive of proximal renal tubule dysfunction. These abnormalities tended to appear after one year of TDF therapy then persisted.

Of note, there were no fractures or other clinical "bone events" reported for any subject receiving TDF up to the data cut-off date for the week 96 interim trial report.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4 above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common clinical AEs occurred in 82 subjects, 41/48 (85%) in the TDF group and 41/49 (84%) in the d4T or ZDV group, respectively. The highest frequency of such AEs were reported in the SOC Infections and Infestations. Table 17 shows the range of common clinical AEs, including all AE grades reported (Note: all were Grade 1 and 2; there were no Grade 3 or 4 AEs reported in the randomized treatment period). Nasopharyngitis was prominent (34% overall), followed by cough (12%) and otitis media (11%).

Table 17. Common Adverse Events Reported for ≥ 5% of Subjects in the Randomized Treatment Period (Weeks 0 to 48)

Adverse Events Preferred Term	**TDF* N=48 n (%)**	**d4T or ZDV N=49 n (%)**	**Total N=97 n (%)**
Allergic rhinitis	4 (8)	0	4 (4)
Cough	6 (13)	6 (12)	12 (12)
Diarrhea	4 (8)	1 (2)	5 (5)
Gastroenteritis	3 (6)	4 (8)	7 (7)
Nasopharyngitis	16 (33)	17 (35)	33 (34)
Otitis media	7 (15)	4 (8)	11 (11)
Pharyngotonsillitis	2 (4)	1 (2)	3 (3)
Pyrexia	1 (2)	3 (6)	4 (4)
Sinusitis	3 (6)	1 (2)	4 (4)
Upper respiratory tract infection	6 (13)	3 (6)	9 (9)
Vomiting	6 (13)	0	6 (6)

The Viread label cites rates of common AEs in adult patients in previous treatment trials. AEs that have been reported in ≥ 2% of treatment-experienced adult subjects include diarrhea (11%) and vomiting (4%). The other common AEs noted in Trial 0352 were not reported in postmarketing, and this may be because many of them might be expected to occur largely in children alone (e.g. nasopharyngitis, otitis media, allergic rhinitis, and pharyngotonsillitis). In summary, no concerning new AEs were reported in this pediatric trial.

Relationship to Trial Drug

The applicant determined that there were five subjects in the TDF group and one in the d4T or ZDV group who experienced AEs that were related to trial drug. These AEs included vomiting (3 subjects in TDF group), gastritis, nausea and enuresis (1 subject each in TDF group), and maculopapular rash (1 subject in d4T or ZDV group).

7.4.2 Laboratory Findings

Overall, there were no significant differences between treatment groups reported in the laboratory profile, in the randomized treatment period (Weeks 0 to 48). The majority of abnormalities were Grade 1 and Grade 2 in severity, as shown in Table 18.

Table 18. Treatment-Emergent Laboratory Abnormalities by Toxicity Grade, Randomized Treatment Period

Toxicity Grade	**TDF N=48 n (%)**	**d4T or ZDV N=49 n (%)**
Grade 1	31 (65)	21 (43)
Grade 2	14 (29)	23 (47)
Grade 3	3 (4)	5 (10)
Grade 4	1 (2)	0

Grades 3 and 4 abnormalities were reported for four subjects in the TDF group and five subjects in the d4T or ZDV group during the randomized treatment period. Grades 3 and 4 abnormalities were most frequently reported for amylase (two subjects in each group), and neutrophil count (two subjects in the d4T or ZDV group), as shown in Table 19.

Table 19. Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities, Randomized Treatment Period

Laboratory Abnormality	**TDF N=48 n (%)**	**d4T or ZDV N=49 n (%)**
Neutrophil count	0	2 (4)
Amylase	2 (4)	2 (4)
Lipase	1 (2)	0
Hyperglycemia	1 (2)	0
Total cholesterol	0	1 (2)
TOTAL	**4**	**5**

Comparing these findings with data from the Viread label, there appears to be consistency in the nature of the Grade 3 or 4 laboratory events that occurred in the pediatric population and the adult population. Study 907 (adults) reported Grade 3 or 4 laboratory abnormalities in ≥ 1% of Viread-treated subjects at Week 48 for triglycerides (11%), creatine kinase (12%), serum amylase (7%), glycosuria (3%), AST (4%), ALT (4%), serum glucose (3%), and neutrophils (2%). The findings from Trial 0352 show similar abnormalities, albeit at a lower frequency. Other than single reports of total cholesterol and lipase, no new laboratory abnormalities of concern were seen in this pediatric trial.

7.4.3 Vital Signs

All enrolled subjects had vital signs assessed as part of the initial workup, and vital sign collection was performed per protocol at each trial visit. The applicant provided summary statistics for vital signs. There were no significant abnormalities reported.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained as a routine part of the assessments carried out in this trial.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

Immunogenicity was not assessed in this trial.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This aspect was not assessed as only a single dose level was administered.

7.5.2 Time Dependency for Adverse Events

Adverse events were assessed throughout the 48-week randomized treatment period and 96-week extension period. No specific time-dependency was identified.

7.5.3 Drug-Demographic Interactions

There were too few specific AEs to allow assessment of drug-demographic interactions.

7.5.4 Drug-Disease Interactions

As with adults who take TDF, it appears that HIV disease was treated appropriately with the administration of TDF as part of a HAART regimen. This was evidenced by the general decrease in HIV-1 RNA level in subjects over time during the treatment period, as well as the improvement in CD4 cell count and percent, changes that occurred across age groups.

7.5.5 Drug-Drug Interactions

All subjects were on more than one other drug during the trial (HAART). No formal assessment was made of the drug interactions between TDF and these other drugs, but it is expected that drug-drug interactions in pediatric subjects will not be significantly different from those seen in adults (please see Viread label).

7.6 Additional Safety Evaluations

Viread is an approved drug, and this submission did not, therefore, contain any pre-clinical data or analysis.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

See section 7.3.4, Bone Events. Both weight gain and age-appropriate increased in height were reported over the course of the trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

Due to safety concerns for bone events in pediatric patients 0 to 2 years of age, DAVP has been waiting for completion and review of trials in the 2 to <18 years age group before determining whether it is appropriate to study tenofovir DF in this age group. The review of the data and discussions regarding potential trials in subjects 0 to 2 years of age, are ongoing.

8 Postmarket Experience

DAVP and OSE are continuously monitoring post-marketing AEs and reviewing specific events as needed.

9 Appendices

9.1 Literature Review/References

1. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

9.2 Labeling Recommendations

As of this review date, labeling negotiations with the applicant are not yet completed. The clinical labeling recommendations completed thus far have been sent to the applicant. The most relevant pediatric labeling information is included below. Please refer to the CDTL Review for additional details.

2.2 Recommended Dose in Pediatric Patients (2 to Less Than 18 Years of Age)

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 tablets. The dose is one tablet once daily taken orally, without regard to food.

6.1 Adverse Reactions from Clinical Trials Experience

Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection

Of 89 pediatric subjects who received VIREAD in the randomized or open label phases of Study 352 (median exposure of 104 weeks), 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)]*.

8 USE IN SPECIFIC POPULATIONS

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 incorrectly 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 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.

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with VIREAD (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the VIREAD and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to VIREAD and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of VIREAD in pediatric patients 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to VIREAD. *[See Warnings and Precautions (5.6), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].*

Safety and effectiveness of VIREAD in pediatric patients younger than 2 years of age have not been established.

9.3 Advisory Committee Meeting

There will be no Advisory Committee meeting convened for this sNDA.

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

/s/

TAFADZWA S VARGAS-KASAMBIRA
12/23/2011

LINDA L LEWIS
12/23/2011