CENTER FOR DRUG EVALUATION AND RESEARCH

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 4, 2012
From	Linda L. Lewis, M.D. Medical Officer Team Leader DAVP/OAP/CDER/FDA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22577/000 NDA 21-356/SE-038
Applicant	Gilead Sciences, Inc. Foster City, CA
Date of Submission	July 18, 2011
PDUFA Goal Date	January 18, 2012
Proprietary Name / Established (USAN) names	Viread Tenofovir disoproxil fumarate
Dosage forms / Strength	Tablets: 150, 200, 250, and 300 mg Oral powder: 40 mg/g powder
Proposed Indication(s)	Treatment of HIV-1 infection in pediatric patients 2 to less than 12 years of age
Recommended:	*Approval, tentative recommendation pending resolution of oral powder CMC inspection issues*

1. Introduction

Tenofovir disoproxil fumarate (TDF, Viread) is an oral pro-drug of tenofovir, a synthetic nucleotide that inhibits both HIV-1 reverse transcriptase and hepatitis B virus (HBV) polymerase. It received accelerated approval (under 21 CFR 314 Subpart H) for use in the treatment of HIV-1 infection in adults in October, 2001. Confirmatory trials supported the early trial results and TDF received full, traditional approval (under 21 CFR 314.510) in March, 2006. Since the time of the original NDA approval, TDF has become one of the most frequently prescribed drugs for HIV-1 infection in adults and has also been approved as part of three fixed dose combination products, Truvada (TDF+emtricitabine), Atripla (TDF+emtricitabine+efavirenz), and Complera (TDF+emtricitabine+rilpivirine). In addition, TDF was approved for treatment of adults with chronic HBV infection in August, 2008, and is also widely prescribed for that indication.

The Applicant has had an ongoing pediatric drug development program that began prior to the initial approval of TDF. Gilead was encouraged to develop TDF for both HIV and HBV indications in pediatric patients (see Section 10 for a description of pediatric plans). Because of concerns regarding the potential for bone toxicity, the Division of Antiviral Products Review Team recommended cautious introduction of the drug into pediatric patients only after the nature and extent of bone toxicity had been carefully evaluated in adult patients with HIV. Adult clinical trials documented losses in bone mineral density (BMD) in the first year of TDF dosing, followed by relatively stable measurements thereafter, but did not suggest rapid or progressive BMD changes in adults. In addition, some biochemical markers of bone metabolism such as parathyroid hormone (PTH) levels also appeared to be affected. Postmarketing reports of renal tubulopathy including Fanconi syndrome were also associated with TDF use, although renal abnormalities were rarely observed in the clinical trials. The exact mechanism of the BMD loss has not been fully explained but some of the bone effects may be related to renal tubular dysfunction and urinary phosphate wasting.

2. Background

The Applicant began Phase I/II studies in pediatric patients with a small, open label, carefully monitored pilot study to evaluate pharmacokinetics (PK) and safety. Study 926, conducted at the National Institutes of Health, documented significant decreases in HIV-1 RNA in heavily treatment-experienced pediatric patients receiving TDF 175 mg/m^2 once daily (using investigational 75 mg tablets, no longer available) in combination with other antiretroviral drugs. In that cohort of 18 subjects 4 to 18 years of age, four subjects experienced decreases > 6% in lumbar spine BMD. As observed in the adult clinical trials, the decreases in BMD were observed in the first 24-48 weeks of dosing but did not progress after that with continued dosing.

Study 926 provided the basis for dose selection for larger pediatric trials in both HIV-1-infected adolescents (Study 0321) and in pediatric HIV patients 2 to 12 years of age (Study 0352). The Applicant initially planned to submit both Study 0321 and Study 0352 simultaneously. At the time of the pre-NDA meeting for the initial pediatric supplement in July, 2009, the Applicant notified the Review Team that Study 0352 had failed to achieve its primary efficacy endpoint as calculated using the time-to-loss-of-virologic-response (TLOVR) analysis. They presented information regarding factors likely to have contributed to the observed lack of efficacy and were encouraged to reevaluate the data and submit the complete Study 0352 data for review in a later supplement. The FDA Review Team suggested the Applicant repeat the efficacy analysis using the currently preferred "snapshot" analysis (HIV RNA < 400 or < 50 copies/mL at specific 48 week time window).

The current submissions provide the 48 week clinical study report and datasets for Study 0352, seek an indication for treatment of HIV-1 in the 2 to less than 12 years age group, and proposes labeling describing the PK, safety, and efficacy results of the study. In addition to the clinical data, the submission to NDA 22577 provides CMC data for a new

oral powder formulation and a bioequivalence study (Study 0312) demonstrating the similarity in exposure between the oral powder and the approved 300 mg tablets. The supplement to NDA 21356 provides CMC data on new reduced-strength tablets of 150 mg, 200 mg, and 250 mg. These smaller tablets are similar in composition to the approved 300 mg tablets. Both formulations (oral powder and tablets of multiple strengths) are included in a single product label and dosing recommendations appropriate are provided for the two formulations across the pediatric age range greater than 2 years of age.

3. CMC/Device

These submissions contain new CMC information regarding TDF oral powder and reduced-strength tablets. For a full description of the CMC issues related to the oral powder please refer to the CMC Review performed by Dr. Rao Kambhampati. The oral powder represents a new, age-appropriate formulation for patients unable to swallow tablets. Viread Oral Powder is white, microencapsulated, taste-masked granules containing 40 mg of TDF per gram of the powder. The TDF drug substance is the same as is used in the manufacture of the approved tablets. Oral powder is produced by (b) (4)

The bulk powder is re-blended and packaged with a Viread dosing scoop that delivers 1 gram of powder per level scoop and is embossed with a "½" scoop measuring line. The appropriate dose (according to patient weight) of granules is mixed in a semi-soft food vehicle such as apple sauce or yogurt and administered to the patient. The granules do not completely dissolve in the vehicle but if not administered quickly, enough of the taste-masking is removed to make the mixture taste bitter. Stability data for the finished oral powder supported an expiration dating period of 36 months, stored at 25°C.

As noted above, the reduced-strength tablets are similar in composition to the approved adult strength tablets and, consequently, are manufactured using the same processes as the currently approved tablets. For a complete review of the CMC data submitted to support the approval of the reduced-strength tablets, please refer to the review performed by Dr. Jean Salemme. Most of the CMC processes approved for the 300 mg tablets will be used in manufacturing the reduced-strength tablets. However, the CMC/Biopharmaceutics reviewer, Dr. Arzu Selen, considered the dissolution test acceptance criterion approved for the 300 mg tablets too liberal for the smaller, reduced-strength tablets (b) (4) She recommended a dissolution test acceptance criterion of Q= (b) (4) in 20 minutes, rather than the Q= (b) (4) in 30 minutes approved for the 300 mg tablets.

Multiple manufacturing sites involved in the production of TDF oral powder were inspected by FDA Office of Compliance staff. Inspections have been completed although not all full reports are available at the time of this review. The Office of Compliance notified the Review Team of a potentially significant issue identified at the

site manufacturing the bulk oral powder (Aptalis, previously known as Eurand). The summary description of the problem noted, "The Viread pediatric drug product manufacturing process requires   (b) (4)

During the facility inspection carried out last week, the investigator observed that   (b) (4)

The total granule blend strength looks OK. The concern here is that if there   (b) (4)

In addition, the site could not document why the oversized granules contain a higher proportion of API compared to the correctly sized granules. This issue and others mentioned in the 483 issued to the site remain under active review and have not been resolved at the time of this review.

We have also been notified that a Gilead Sciences site in Ireland (where packaging of bulk powder into bottles is performed) was inspected and some deficiencies were identified. A 483 was issued to the site and the site has provided written responses which are currently under review by the Office of Compliance staff. The nature of these deficiencies has not been communicated to the clinical Review Team.

The CMC reviewers confirm that the formulation used in the pediatric clinical trial was the same formulation planned for commercial use. Therefore, all PK, safety and efficacy data from the trial reflect these noted CMC issues. From the clinical perspective, if the noted CMC inspection deficiencies had clinical implications, they must be relatively minor given the good results documented in the trial. My recommendation for approval of Viread oral powder is, however, contingent on resolving the CMC inspection issues and developing controls for this process that limit the potential for inaccurate dosing of Viread oral powder.

4. Nonclinical Pharmacology/Toxicology

Extensive non-clinical studies evaluating the pharmacology, mechanism of action, metabolism, and toxicology profile of TDF were submitted and reviewed for the original NDA approval. For this supplement, the applicant did not provide any new non-clinical pharmacokinetic or toxicology studies. For a detailed discussion of the non-clinical pharmacology/toxicology data previously submitted, please refer to the review performed for the original NDA submission by Dr. Pritam Verma. In addition, Dr. Mark Powley reviewed toxicologic information relevant to the maximum amount of ethylcellulose that might be consumed by a pediatric patient receiving the highest dose. Although toxicology studies are limited, he concluded the high doses of ethylcellulose are likely to

be associated with minimal risk of toxicity other than gastrointestinal effects (i.e., "laxative effects").

5. Clinical Pharmacology/Biopharmaceutics

To bridge use of the approved Viread tablets and the new oral powder, the Applicant submitted a bioequivalence study comparing 300 mg of the oral powder to the approved tablet and PK data from a subset of subjects enrolled in Study 0352. For a complete description of the clinical pharmacology studies relevant to pediatric dose selection and the PK results obtained in Study 0352, please refer to the Clinical Pharmacology Review submitted by Dr. Dionna Green.

Results from both Study 926 and another small single dose PK study suggested that a dose of 8 mg/kg once daily should provide appropriate dosing in pediatric patients and match the adult exposure found to be effective. Thus, this dose was selected for further evaluation in a larger PK, safety and efficacy study (Study 0352). Intensive PK assessments were performed in a substudy of 23 subjects enrolled in Study 0352 and included AUC, C_{max}, and other PK parameters following 4 weeks of dosing. Values in the pediatric subjects were found to be slightly lower than corresponding parameters in adults; 11% lower in subjects 2 to < 6 years of age and 18% lower in subjects 6 to < 12 years of age. Exclusion of a single outlier subject in the 6 to < 12 years age group resulted in a group exposure only 12% less than in adults. Dr. Green noted that the earlier adult PK data were obtained following a high-fat meal, conditions known to increase exposure, while the pediatric PK assessment did not specify meal type and the difference in food effect may account for much of the observed difference in exposure. Current approved dosing recommendations no longer recommend TDF administration with food. In addition, when Dr. Green divided pediatric subjects into high, mid, and low exposure cohorts, no clear correlation between AUC and clinical outcome was identified. Finally, Dr. Green noted that when normalized for weight, tenofovir clearance was similar across the 2 to < 12 year age range. She concluded the dose of 8 mg/kg given once daily was the appropriate dose to achieve exposure similar to those shown to be safe and effective in adults.

The bioequivalence study, Study 0312, was conducted in healthy adult volunteers using an appropriate study design. This study showed that the two formulations were quite similar in terms of overall exposure (geometric least-squares mean ratio for AUC_{inf} of powder compared to tablet was 92%) but C_{max} was lower for the oral powder (ratio 73%). The difference is likely due to   (b) (4)
                                Because the bioequivalence study and the PK data from Study 0352 were considered pivotal for this review, the clinical site conducting the bioequivalence study, the bioanalytic laboratory, and one of the clinical sites participating in the PK substudy were inspected by Office of Compliance staff. Data from two subjects in the bioequivalence study were deemed unacceptable and data from these subjects were excluded from the final analysis; exclusion did not affect conclusions.

The Review Team agreed with the Applicant's proposed dosing recommendations based on results of the clinical trials submitted. Dosing of both formulations is based on a target dose of 8 mg/kg up to a maximum dose of 300 mg but must accommodate the oral powder dosing device/scoop (one scoop=40 mg) and the 50 mg increments of the reduced-strength tablets (see Tables 1 and 2). These dose recommendations will be displayed in the product label.

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

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: VIREAD Tablets Dosing Recommendations for Pediatric Patients Able to Swallow Tablets, ≥2 Years of Age, and Weighing ≥17 kg

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

6. Clinical Microbiology

Tenofovir (TNF), the parent compound and active metabolite of TDF, is a nucleotide analogue of adenosine 5'-monophosphate. TNF undergoes further intracellular phosphorylation and produces its antiviral effect by competing with the natural nucleotide being incorporation into DNA by HIV-1 reverse transcriptase and HBV polymerase. It lacks the hydroxyl group that allows addition of subsequent nucleotides and therefore acts as a chain terminator in DNA synthesis in both viruses.

In previous nonclinical and clinical studies, the K65R substitution in the reverse transcriptase gene was identified as a mutation leading to TDF resistance. In addition, patients with HIV-1 containing three or more thymidine-analog resistance associated mutations (TAMs) including M41L and L210W have been shown to have a reduced response to TDF.

The Applicant conducted a virology/resistance substudy in subjects who discontinued study drugs because of virologic failure or had HIV-1 RNA > 400 copies/mL at Weeks 48, 96 or 144. Baseline genotyping could not be performed in Study 0352 because all subjects had very low HIV-1 RNA at the time of study entry but genotyping was performed on 19 (2 with unsuccessful genotype assays) of the 89 subjects who received TDF either initially or after rolling over to open-label drug. No new substitutions associated with TDF resistance were identified during the study. One subject (#3106-9097), had increasing HIV-1 RNA levels at Week 2 and had substitutions at Y181C and K65R identified in the Week 4 genotyping sample. This subject had previously received treatment with ZDV, abacavir, lamivudine (3TC), and nevirapine and was infected with subtype A HIV-1. Dr. Narayana Battula, the Microbiology Reviewer considered this rapid development of resistance substitutions most likely to be indicative of emergence of pre-existing, archived resistance but could not rule out development of resistance after the initial switch to TDF. In addition, 12 subjects developed the M184V substitution associated with 3TC and emtricitabine resistance and 4 subjects developed TAMs (all also had M184V).

For a more complete description of the virologic assessments conducted as part of this supplement, please refer to the Microbiology Review submitted by Dr. Battula.

7. Clinical/Statistical- Efficacy

For a complete description of the study design and enrollment criteria, please refer to the Clinical Review submitted by Dr. Tafadzwa Vargas-Kasambira. For detailed description of the statistical analyses and conclusions, please see the Statistical Review completed by Dr. Wen Zeng.

Of 97 subjects enrolled in Study 0352, 92 completed the 48 week randomized phase of the study (44/48 in TDF arm and 48/49 in the ZDV/d4T arm) and 79 subjects entered the

open-label TDF phase. In the TDF arm, one subject had an increase in viral load, one subject's parents stopped dosing, one subject withdrew consent because of not liking the oral powder and one subject withdrew consent because unable to comply with study procedures. In the ZDV/d4T arm, one subject withdrew consent because of refusal to undergo DEXA evaluations.

The primary efficacy endpoint for Study 0352 was the HIV-1 RNA < 400 copies/mL using a TLOVR analysis. Multiple secondary efficacy endpoints were also evaluated. The choice of endpoints was discussed with the applicant at meetings held prior to initiation of the pediatric Phase 3 trials and TLOVR was considered acceptable for an HIV efficacy trial at that time. Since initiation of Study 0352, the FDA has revised recommendations for analysis of efficacy and currently suggests sponsors use an analysis that evaluates proportion of subjects with HIV-1 RNA < 400 at a specific time window (the "snapshot method"), usually after 48 weeks of treatment. At the pre-NDA meeting in 2009, the Review Team recommended use of the snapshot analysis and also submission of the longer-term efficacy at Week 96.

The study failed to demonstrate that TDF was non-inferior to remaining on ZDV or d4T using the TLOVR analysis. Using this analysis (M=F, ITT population), 83.3% (40/48) of subjects in the TDF arm compared to 91.8% (45/49) of those in the ZDV/d4T had HIV-1 RNA < 400 copies/mL at Week 48. The estimated difference between the two arms was -8.5% with 95% confidence interval -21.5% to 4.5% which missed the pre-defined 15% non-inferiority margin.

However, using the currently recommended snapshot analysis, 87.5% (42/48) of subjects in the TDF arm had HIV-1 RNA < 400 copies/mL at Week 48 compared to 87.8% (43/49) in the ZDV/d4T arm. The difference between arms was estimated at -0.3% with 95% CI of [-13.4% to 12.9%]. Of the 97 subjects initially enrolled and randomized subjects, 5 were between 12 and <16 years of age, in violation of protocol enrollment criteria. If these 5 subjects are excluded from the snapshot analysis, the rate of HIV-1 RNA < 400 copies/mL was 88.6% (39/44) in the TDF arm and was 89.6% (43/48) for the ZDV/d4T arm. This estimated difference is -0.9% with 95% CI of [-13.7%, 11.8%]. Thus, using the snapshot analysis either including or excluding the protocol violation subjects, the study met the criteria for non-inferiority. In an important secondary analysis performed using the more stringent endpoint of HIV-1 RNA < 50 copies/mL at Week 48, virologic success was achieved in 75% of subjects in the TDF arm and 79.6% of those in the ZDV/d4T arm (difference -4.6%, [95% CI -21.2% to 12.1%]) . Although again, the TDF arm did not reach statistical non-inferiority in this secondary analysis, these results are remarkably good.

The long-term Week 96 efficacy data support persistence of the treatment response to TDF as part of an HIV treatment regimen. Of the 79 subjects who entered the open-label phase of the study after completing Week 48, 66 (38 remaining on TDF and 28 rolling from ZDV/d4T to TDF) completed treatment through Week 96 and 86.4% continued to have HIV-1 RNA < 400 copies/mL. The trial is ongoing with all remaining subjects continuing to receive TDF as part of their HIV treatment regimen.

Subgroup analyses of efficacy were performed according to gender, race/ethnicity, age and geographic region. As noted in the Statistical Review, no significant differences in the proportion of subjects with viral suppression (HIV-1 RNA <400 copies/mL at Week 48) were identified based on gender, age, race/ethnicity, or location (US vs. non-US). However, caution is recommended in interpreting these results because of the small size of the trial, especially some subgroups. Differences in treatment benefit for specific subgroups have not been identified in adult clinical trials.

All of the analysis methods lead to estimates of successful viral suppression in > 80% of subjects in this pediatric population with suppressed HIV-1 RNA at entry to Study 0352. These subjects had been on treatment for variable lengths of time and had received a variety of different regimens prior to enrollment in the trial. I attribute the failure to achieve non-inferiority using the TLOVR efficacy to the relatively small number of subjects enrolled in the study and the high rate of success in the control arm. Our experience with clinical trials of this design (the "switch study" design) suggests that the test arm frequently loses because, invariably, a number of subjects drop out due to adverse events or intolerance of the new test regimen but subjects remaining on their original regimen have already proven that they tolerate that regimen and rarely drop out for these reasons. In the TLOVR analysis of Study 0352, the small number of subjects who failed to complete the trial had a major impact on the difference between the two arms. Based on understanding of virus replication and data from adult clinical trials, I expect TDF to provide virologic benefit in a combination antiretroviral regimen in adolescents whose HIV-1 is reported to be susceptible to the drug.

8. Safety

The safety profile of TDF in adult patients with HIV-1 infection has been well-characterized. In the adult HIV-1 treatment trials, the most commonly reported adverse events of moderate to severe intensity were: rash, diarrhea, headache, pain, depression, asthenia, and nausea. The toxicities of greatest concern, however, are the more uncommon occurrences of renal and bone toxicity. While reports of renal toxicity were rare in the adult clinical trials, bone effects were documented in the adult Phase 3 study by DEXA and bone biochemical marker monitoring. In addition to routine hematologic and serum biochemical tests, Study 0352 included sequential DEXA scans to assess BMD and measurements of biochemical markers of bone metabolism. Dr. Stephen Voss in the Division of Reproductive and Urologic Products provided consultation regarding the analysis of bone effects for this supplement (see DRUP Consult, dated November 18, 2011). Dr. Voss' findings and conclusions are summarized in this review. For a complete review of the clinical and laboratory safety data in Study 0352, refer to the Clinical Review performed by Dr. Vargas-Kasambira; the Clinical Review focuses on the initial randomized 48 weeks during which comparisons can be made.

No deaths occurred in Study 0352 and the four reported serious adverse events (SAEs) were evenly divided across the treatment arms. None of the SAEs were considered

related to randomized study drug and included: asthmatic crisis, lymphadenitis, pneumonia and pharyngotonsillitis. No subjects discontinued study drug because of clinical or laboratory adverse events and no clinical AEs of Grade 3 or 4 (severe or life-threatening) were reported during the initial randomized 48 weeks.

Mild to moderate clinical AEs were common in the initial randomized phase of Study 0352, occurring in 85% of subjects in the TDF arm and 84% of those in the ZDV/d4T arm. Table 3, abstracted from Dr. Vargas-Kasambira's Clinical Review, displays the most commonly reported clinical AEs during this phase of the trial. Many of these AEs are expected as they are common pediatric conditions and illnesses, such as nasopharyngitis, otitis media, and upper respiratory infections. AEs observed in at least 5% more of the TDF arm than the comparator arm are highlighted.

Table 3: Common Adverse Events Reported for ≥ 5% of Subjects in the Randomized Treatment Period (Weeks 0 to 48)

Adverse Events Preferred Term	TDF N=48	d4T or ZDV N=49	Total N=97
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)

Source: Abstracted from Clinical Review, page 41, by Dr. Vargas-Kasambira.

Minor laboratory abnormalities were similarly common across both treatment arms but more significant Grade 3 or 4 laboratory abnormalities occurred in very few subjects. Two subjects in each arm developed Grade 3/4 elevated amylase, 1 TDF subject had elevated lipase and 1 had hyperglycemia. Two subjects receiving ZDV/d4T had Grade 3/4 neutropenia and one had elevated total cholesterol.

Study 0352 provided extensive monitoring for bone effects including DEXA scans every 6 months and biochemical markers of bone metabolism. The results of the bone monitoring in this study must be interpreted in the context of growing children who should be increasing BMD rapidly. In the previously reviewed Study 0321 in adolescent subjects 12 to > 18 years of age, TDF appeared to have negative effects on BMD and increases in markers of bone turnover similar to those observed in adults. Of note, however, use of TDF did not appear to affect bone growth (i.e., height).

As noted in Dr. Voss' consult, the subjects enrolled in Study 0352 had baseline BMD significantly below the reference age-matched population as well as negative baseline height and weight z-scores. In general, the 2 to <12 year old subjects maintained their baseline spine Z-scores over 3 years of TDF exposure. However, total body BMD appeared to be negatively affected by TDF exposure. During the randomized phase of the trial, the TDF arm had lower BMD gains than the ZDV/d4T arm at 24 and 48 weeks. This TDF-control difference was statistically significant for the overall study population. This was unlike the previous adolescent study, in which there were no statistical differences between TDF and control. In the open-label phase of Study 0352, total body Z-scores declined progressively, unlike lumbar spine, but similar to the previous adolescent study. Markers of bone resorption (serum N-telopeptide and C-telopeptide), bone formation (serum osteocalcin and bone-specific alkaline phosphatase) increased in the TDF arm compared to the ZDV/d4T arm over 48 weeks indicating increased bone turnover and parathyroid hormone increased in the TDF arm compared to the control arm. As in the previous adolescent trial, height and weight z-scores were maintained suggesting no effect on bone growth.

Five subjects in Study 0352 met the Applicant's search criteria suggestive of possible proximal renal tubulopathy. These subjects had at least two of five key abnormalities (proteinuria, glycosuria, hypophosphatemia, low serum bicarbonate, and hypokalemia) in addition to a reduction in creatinine clearance > 35% from baseline. Four of these subjects discontinued TDF because of these AEs (all after the initial randomized 48 weeks); three had hypophosphatemia and one had glycosuria. Three subjects had significant proximal renal tubulopathy with hypophosphatemia, increased markers of bone turnover, and significant declines in both spine and total body BMD Z-scores. This proportion of subjects with the combination of proximal tubulopathy and significant bone toxicity (3 of 89 or 3.4% of subjects followed beyond 48 weeks) is higher than has been observed in other clinical trials but may be reflect the low baseline BMD status of this study population.

Overall, the safety data collected in pediatric subjects 2 to < 12 years of age enrolled in Study 0352 revealed a safety profile very similar to that observed in adult and adolescent subjects. Pediatric-specific data from the bone and renal safety monitoring will be included in the product label but otherwise the safety profile will reference the larger adult safety database.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held regarding this supplement.

10.   Pediatrics

As noted in Section 2, the Applicant has ongoing pediatric development programs for TDF for both HIV and HBV indications. Gilead has pediatric Postmarketing

Requirements (PMRs) under PREA for Viread for both HIV and HBV treatment indications and was also issued separate Written Requests for Pediatric Studies for treatment of HIV and HBV.

Development of a stable, palatable, age-appropriate formulation has been challenging but the powder/granule formulation was developed and used in this clinical trial of HIV-infected pediatric patients. Evaluation of TDF in HIV-infected patients younger than 2 years has been deferred. Because of safety concerns in the youngest age group and the potential for bone toxicity in rapidly growing infants and young children, we recommended the study in 2 to 12 year old subjects be completed and reviewed before determining whether to require study of TDF for HIV in the newborn to 2 years age group.

The Applicant also has an active pediatric development program of TDF as treatment for chronic HBV infection. Studies have been initiated in HBV-infected pediatric patients 12 to less than 18 years of age and the applicant has submitted a draft protocol synopsis for evaluating patients 2 to less than 12 years of age. According to experts in managing HBV (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this group may be waived in the future if this continues to be the consensus opinion at the time the safety data is available or if the risk/benefit assessment is not favorable based on safety data from older pediatric patients.

In this submission, the Applicant has updated their pediatric development plan and again requested a deferral of evaluation in the youngest age group. This request was reviewed with the Pediatric Review Committtee (PeRC). After review of the bone safety data available in this submission, we and the PeRC agree that deferral is appropriate since the current supplement in patients 2 to less than 12 is ready for approval. We do not believe the available safety data precludes continuing careful study of TDF in patients less than 2 years of age, although we acknowledge there is little age-appropriate reference data for some of the bone biomarkers proposed for monitoring. No new requirements for pediatric studies under PREA are triggered by this submission.

The current submission is intended to fulfill the remaining components of the pediatric study requirements of the WR for the HIV indication. The Applicant requested an exclusivity determination at this time, as the WR did not include a request for evaluation of patients less than 2 years of age. The Exclusivity Board discussed the submitted pediatric trials on September 6, 2011, and determined that the conditions of the WR had been met; exclusivity was granted.

11.   Other Relevant Regulatory Issues

There are no other relevant regulatory issues that need to be addressed for this supplement.

12.   Labeling

The Applicant has proposed addition of the pediatric age range 2 years and over to the HIV treatment indication and includes dose recommendations for both Viread oral powder and reduced-strength tablets in the Indications and Usage section (1.1) and the Dosage and Administration section (2.2) and has updated the Clinical Pharmacology section with the PK data from Study 0352. A brief description of Study 0352 is included in the Use in Specific Populations section (8.4) and information related to the bone effects observed in pediatric patients is included in the Warnings and Precautions section (5.6). Major revisions or new text are included below in *italics*.

The Indications and Usage section will be revised to include pediatric patients as follows:

> 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.*

The Dosage and Administration section will be amended to include dose recommendations for pediatric patients and directions on how to administer the oral powder as follows:

> *2.2 Recommended Dose in Pediatric Patients (2 to Less Than 18 Years of Age)*
>
> *For the treatment of HIV-1 in pediatric patients 2 years of age and older, the recommended oral dose of VIREAD is 8 mg of tenofovir disoproxil fumarate per kilogram of body weight (up to a maximum of 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.*

> Dosing tables for the two formulations are shown in Section 5 of this review.

The Warnings and Precautions section, Decrease in Bone Mineral Density (section 5.6), was revised to include description of the results of bone monitoring in pediatric subjects in Study 0352 as follows:

> Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients *[previous age range deleted]* 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. In clinical stud*ies evaluating VIREAD in* HIV-1 infected pediatric subjects *2 to <18* years of age, bone effects were similar to *those observed in* adult subjects. Under normal circumstances BMD increases rapidly in *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.* (b) (4)

> In *Study 321 (12 to <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 (>4%) lumbar spine BMD loss *at Week 48. Changes from baseline in BMD Z-scores 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 suggest increased bone turnover, consistent with the effects observed in adults.

> The concluding paragraphs in this section remain unchanged.

The following description of the safety information will be included in the Adverse Reactions from Clinical Trials (section 6.1):

> Assessment of adverse reactions is based on *two* randomized trials (*Studies 352 and 321*) in *184* HIV-1 infected pediatric subjects (*2 to less than 18 years of age*) who received treatment with VIREAD (*N=93*) or placebo/*active comparator (N=91)* 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 *2* 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)].

The DAVP Review Team agreed with placing the description of Study 0352 in Section 8.4 (Use in Specific Populations, Pediatric Use). The proposed study description was revised to include more information regarding the study population, subjects excluded from the analysis, and subjects who prematurely discontinued study drug.

The safety of VIREAD in pediatric patients aged *2* to less than 18 years is supported by data from *two* randomized trials in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients *2* to less than 18 years of age at the recommended doses 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.

The description of Study 0321 remains unchanged.

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

The PK data from Study 0352 has been added to information from Study 0321 in the Clinical Pharmacology, Pharmacokinetics section (12.3):

Pediatric Patients 2 Years of Age and Older: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected pediatric subjects 2 to less than 18 years (Table 11). 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 (± 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} ($\mu g/mL$)	0.38 ± 0.13	0.24 ± 0.13
AUC_{tau} ($\mu g \bullet hr/mL$)	3.39 ± 1.22	2.59 ± 1.06

13. Recommendations/Risk Benefit Assessment

I agree with the Review Team's recommendation to approve TDF (Viread) for the treatment of HIV-1-infected pediatric patients 2 to < 12 years of age. FDA regulations allow approval of drugs for use in pediatric patients on the basis of extrapolation of efficacy from adequate and well-controlled clinical trials in adults when the course of the disease is deemed to be similar in adults and children and the mechanism of action of the drug is considered independent of age and the Applicant provides supporting pediatric data. This is the mechanism by which most antiretroviral drugs are approved for use in pediatrics. In this case, Study 0352 provides some basis for comparing the effectiveness of a TDF-based regimen to regimens including ZDV and d4T, drugs already approved for use in pediatric patients. Although the trial failed to meet its protocol-defined primary efficacy endpoint at 48 weeks, the results were remarkably good in both treatment arms and the TDF arm did achieve non-inferiority to the comparator arm when the FDA's currently recommended analysis was performed. Longer-term (96 week) of open-label TDF documents continued treatment benefit in a high proportion of pediatric subjects remaining in the clinical trial.

In addition, PK and safety data in subjects 2 to < 12 years of age also allow comparison to the larger clinical trials in adults. Drug exposures in this age group were similar to or only slightly lower than those found to be safe and effective in adults. The safety profile was acceptable in the pediatric trial and no new safety concerns were identified in this age group. The potentially serious renal and bone toxicity initially identified in adults receiving TDF was also observed in pediatric subjects. The bone effects of TDF appeared to be similar to those observed in the larger adult clinical trials and a small but potentially significant proportion of pediatric subjects were noted to have a clinical syndrome of hypophosphatemia, proximal renal tubulopathy, and increased bone turnover with loss of BMD. However, the rate of viral suppression in this clinical trial was > 80% regardless of whether subjects switched their ZDV/d4T regimen at the time of initial randomization or after an additional 48 weeks of treatment. Additionally, only four subjects discontinued TDF for any reason before completing 48 weeks of treatment

and only a single subject developed a TDF-associated resistance substitution during the clinical trial (probably emergence of an archived substitution). Therefore, in this age group of patients, the potential benefits of treatment with TDF appear to outweigh the potential risks for those patients whose HIV isolate is expected to be sensitive to TDF.

However, Office of Compliance inspection teams have identified deficiencies at 2 sites involved in the manufacture of Viread oral powder. The sites have been made aware of these issues through 483 forms and are in the process of responding to the inspectors' concerns. My recommendation for approval of this NDA is contingent on the Applicant and all sites providing acceptable responses to the CMC issues and all FDA reviewers and inspectors being assured that the manufacturing process is reliable and predictable. If the CMC issues can not be satisfactorily resolved prior to the PDUFA action date January 18, 2012, a CMC Post-marketing Commitment, a Complete Response, or an extension of the review clock may be needed. Although the reduced strength Viread tablets are identical in composition to the approved 300 mg tablets, the NDA supplement for reduced strength tablets relies on the clinical data from Study 0352 conducted using the oral powder and the two formulations will use a single product label. Therefore, any action taken for the oral powder will also be applied to the reduced strength tablets.