CLINICAL REVIEW

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Established Name	Tenofovir DF (TDF)
(Proposed) Trade Name	VIREAD
Therapeutic Class	HIV-NRTI
Applicant	Gilead
Formulation(s)	Oral tablet
Dosing Regimen	300 mg tablet once daily
Indication(s)	HIV-treatment
Intended Population(s)	Children aged 12- <18 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, the activity and safety data presented in this efficacy supplement of tenofovir disoproxil fumarate (TDF) tablets for the treatment of HIV-1 infection in adolescents aged 12 - < 18 years of age who are ≥ 35 kg support approval.

Overall, the trial failed to show a difference in virologic response between the TDF 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 TDF or OBR. Although changes in HIV-1 RNA in these highly treatment-experienced adolescent subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of TDF in patients ≥12 years of age who weigh ≥ 35 kg and whose HIV-1 isolate is expected to be sensitive to TDF.

1.2 Risk Benefit Assessment

A clear benefit of TDF over placebo was not apparent in this trial due to several factors. However, pharmacokinetic and safety evaluations provide the essential elements of activity and safety of TDF in this pediatric population to allow for approval of TDF by extrapolating efficacy from larger adult trials.

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 patients (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[1]. DAVP agrees that HIV disease in pediatric patients is similar but not identical to

[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 patients, 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 patients, 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).

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 patients 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 patients. 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 patients, 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 patients 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. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

Steady state pharmacokinetic studies of TDF in adolescent subjects provide exposure data consistent with those in adult subjects receiving the approved dose of 300 mg tablet once daily. These data taken together with the lack of new safety signals provide grounds for extrapolating effectiveness of TDF in the right clinical scenarios.

Review of the safety data submitted with this supplement did not identify any unexpected clinical toxicity. As in the adult trials, this adolescent trial suggested that TDF does have effects on bone mineral density (BMD) and biochemical markers of bone turnover; however, the trial was not powered to provide a statistical difference in bone adverse events. The long-term clinical significance of these effects during adolescence is not clear. No new renal events were identified in the adolescent trial, but clinicians should be aware of the known renal adverse events associated with TDF. The identification of the same potential safety risks in adolescents as in adults on TDF did not outweigh the benefit of TDF as a treatment option for either treatment-experienced or treatment-naïve, HIV-infected patients with HIV-1 virus sensitive to TDF.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Safety Post-Marketing Requirement
In study GS-US-104-0321, evidence of impaired bone mineral density (BMD) gains and perturbations of bone deposition and resorption, similar to those identified in the adult HIV-1 treatment trials with VIREAD was observed. Adolescence is a period of rapid bone growth important to adult bone health and the impact of these changes in growing adolescents and younger pediatric patients on future fracture risk is not known. The etiology of VIREAD's bone effects (whether a direct or secondary effect on bone) remains unclear. Based on the clinical trials data and postmarketing reports, the bone effects may be related to proximal renal tubule dysfunction and/or may be due to direct effects on osteoblast and osteoclast function. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We request the Applicant to conduct a controlled study (study of pediatric HBV-infected subjects required under PREA) that elucidates the mechanism of tenofovir's effects on bone. Evaluations of adequate numbers of pediatric subjects must include the following:

a. Measurement of renal excretion of calcium, phosphorous, and magnesium through calculation of the renal phosphate threshold (TmP/GFR).

b. Measurement of urine bicarbonate, urine n-telopeptide, serum bone-specific alkaline phosphatase, parathyroid hormone, osteocalcin, c-telopeptide, 25 hydroxyvitamin D, 1,25 (dihydroxyvitamin) D levels, albumin, calcium, phosphate, magnesium, and bicarbonate.

c. Correlation of renal parameters with measurements of bone mineral density (DEXA).

Consideration will be given to the inclusion of other study parameters deemed appropriate for fulfillment of this PMR.

In addition to this PMR, we request the Applicant to complete the following post-marketing commitment:

Conduct *in vitro* studies in caco-2 cells to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the GI tract, and assess the applicability of the study findings on the observed nonclinical and clinical effects of tenofovir DF on BMD.

2 Introduction and Regulatory Background

2.1 Product Information

Tenofovir disoproxil fumarate (TDF, Viread, (9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate 1:1) is the fumarate salt of a prodrug of tenofovir. TDF is orally bioavailable in humans and is rapidly converted to tenofovir in the presence of human plasma, intestinal homogenate, or liver homogenate. TDF is a nucleotide reverse transcriptase inhibitor (NtRTI) of HIV-1 infection. TDF undergoes two consecutive phosphorylation steps to the active metabolite PMPApp. Both phosphorylation steps are carried out by enzymes that are constitutively active in a variety of cell types. PMPApp is a competitor of deoxyadenosine triphosphate (dATP) and terminates the growing DNA chain. The active intracellular metabolite, PMPApp, inhibits HIV-1 reverse transcriptase.

TDF was originally approved in 2001 for treatment of HIV-1 infection in adults in combination with other antiretroviral agents and currently is approved for treatment of HIV-1 infection in adults (in combination with other antiretroviral agents) and for the treatment of chronic hepatitis B infection in adults. The Applicant is seeking a label indication for TDF in treatment of HIV-1 infected adolescents (aged 12 - <18 years old) at a dose of 300 mg tablets given (b) (4) daily.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Approved NRTIs

3TC / Lamivudine / Epivir
FTC / Emtricibine / Emtriva
ABC / Abacavir / Ziagen
AZT / Zidovudine / Retrovir
DDI / Didanosine / Videx and Videx EC
D4T / Stavudine / Zerit

Fixed dose combinations of some of these medications are also available.

2.3 Availability of Proposed Active Ingredient in the United States

TDF has been marketed for treatment of HIV-1 infection in adults since 2001. It was also approved for treatment of chronic hepatitis B infection in adults in 2009. The current label includes boxed warnings for lactic acidosis and severe hepatomegaly with steatosis and post treatment exacerbation of hepatitis. Other warnings and precautions include new onset or worsening renal impairment including acute renal failure and Fanconi syndrome, decreases in BMD, redistribution/accumulation of body fat, immune

reconstitution syndrome, and early virologic failure in HIV-infected patients on triple nucleoside-only regimens.

2.4 Important Safety Issues With Consideration to Related Drugs

TDF is the only approved nucleotide reverse transcriptase inhibitor (NtRTI) of HIV-1. There are six nucleoside reverse transcriptase inhibitors (NRTI) of HIV-1 currently approved. Triple nucleoside-only regimens are not the preferred treatment regimens for HIV infection as studies have shown that patients on such regimens have had early virologic failure as compared to the preferred treatment regimens of 2 NRTIs and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).

Several warnings in the TDF label including development of lactic acidosis, severe hepatomegaly with steatosis, and immune reconstitution syndrome are class specific warnings and are found in all of the NRTI labels.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pediatric Written Request was granted to Gilead on December 21, 2001 for pediatric trials of TDF in treatment of HIV-1 infected pediatric patients. The Pediatric Written Request included the following requirements: studies of multi-dose PK, safety and activity in combination with other antiretrovirals in treatment experienced pediatric patients following subjects through at least 48 weeks of dosing. Ages of pediatric subjects included those 2-18 years of age. Drug specific safety evaluations were to address gastrointestinal, renal, bone, and growth effects. Bone fractures and healing were to be monitored. Approximately 100 subjects were to be enrolled.

A pre-NDA meeting teleconference was held with the Applicant on July 30, 2009 at which time the preliminary results from the pediatric clinical studies (GS-US-104-321 in adolescents and GS-US-104-0352 in patients aged 2-12 years) were discussed. Several points of discussion follow:

- Both pediatric studies lack conclusive demonstration of efficacy (i.e., both failed to achieve the primary efficacy endpoint). Whether or not these two studies support an indication for TDF in patients 2 to <18 years is a review issue.

- The selected dose of TDF for the 2-12 year old group (8mg/kg) provided a lower TDF exposure than was observed in the adult clinical trials. No other dose was evaluated in this age group.

- The Applicant decided to request an extension of the deadline for the pediatric Written Request for ages 2-12 years and will submit the NDA for this age group when the 96 week data is available for review.

- The agency recommended that the extension time be used to evaluate a higher dose of TDF in the patients remaining in Study 0352.

The Applicant submitted in the current supplemental NDA one of the two pivotal pediatric studies (GS-US-104-0321) with the 48 week results for patients 12 to <18 years of age. In addition, this submission includes final clinical study reports from earlier pilot PK and safety studies of TDF in children: GS-01-926 (96 week data), GS-01-927 (96 week data), and GS-02-938 (single dose). A Safety Update was included after the submission of this sNDA in order to provide a comprehensive review of findings from these studies.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was well organized and inclusive. Additional information was requested regarding drug specific safety concerns (i.e., additional analyses of BMD between groups and detailed descriptions of fractures sustained during the trial). Datasets contained viral load as a logarithmic function but without absolute numbers, so absolute HIV-1 RNA level (copies/mL blood by PCR) data were requested.

3.2 Compliance with Good Clinical Practices

Case report forms (CRFs) were randomly selected and reviewed for completion and appropriateness. Raw datasets were compared to integrated data sets for accuracy of data. Analyses performed by the Applicant were also performed by the review team.

3.3 Financial Disclosures

The Applicant provided appropriate documentation of financial arrangements with clinical investigators per FDA guidance to industry. The Applicant was unable to obtain information regarding potential financial interest or financial agreements for one of the subinvestigators at (b) (6). All other investigators reported they did not have any financial interests or agreements with the Applicant. No specific data integrity issues were raised by these disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The formulation of the drug studied in this trial has already been approved for use in adults and is commercially available.

4.2 Clinical Microbiology

Please refer to Dr. Narayana Battula's Clinical Virology Review.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical data were available for review in this supplemental NDA.

4.4 Clinical Pharmacology

Please refer to Dr. Shirley Lu's Clinical Pharmacology Review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Pediatric TDF Clinical Trials

Type of Study	Study #, Location	Objectives	Design	Study and Control Drug Regimen	Duration	# Subjects	Study/Population Entry Criteria	Status
Efficacy, safety	GS-US-104-0321 18 sites (Brazil 17, Panama 1)	Assess efficacy of TDF plus genotype guided optimized background regimen (OBR) compared with placebo and OBR in HIV-1 infected, antiretroviral treatment experienced adolescents with plasma HIV-1 RNA ≥ 1000 cps/mL	Randomized 1:1, double blind, placebo controlled, multicentered phase 3 study in HIV-1 infected pediatric subjects	Group1: TDF 300mg + OBR Group 2: Placebo + OBR	Ongoing, primary endpoint was 24 weeks	87 randomized and treated (TDF 45, placebo 42); 85 analyzed for efficacy (TDF 44, placebo 41)	Treatment experienced adolescents 12 -<18 years old, weighing ≥35kg, who are failing their current antiretroviral regimen with plasma HIV-1 RNA viral load ≥1000 cps/mL	Completed 48 week data submitted, protocol extension
Safety, PK	GS-01-926 1 site (USA)	Define acute toxicity, safety, tolerability of TDF alone and in combination with other ARVs in HIV infected children Assess the PK profile of	Open label, single and multiple dose PK, 96 week, Phase 1/2 study in HIV infected pediatric	TDF 75mg tablet administered at 175mg/m2 (150, 225, or 300mg/day) as monotherapy	96 wks	18 enrolled, 18 evaluable (single dose PK), 16 evaluable (steady state PK)	HIV-1 infected subjects, aged 4 - <18 years, VL ≥ 10K, failed at least 2 prior ARV regimens	Complete

		TDF in children when given as monotherapy and in combination with other ARVs Define biologically active dose of TDF in HIV infected children Assess immunologic, virologic and clinical effects of TDF administered to HIV infected children alone and in combination with other ARVs	subjects	for 1 wk then with ≥ 2 ARVs, with food				
Safety, PK	GS-01-927 1 site (France)	Safety of TDF when given in combination with other ARVs in pediatric patients with advanced HIV Assess single dose and steady-state PK following TDF 75, 150, 225, or 300mg once daily alone or as part of combination ARV regimen Target TDF exposure in children based on exposure in adults with 300mg TDF dose based on single dose PK	Open label single dose and multiple dose PK, 96wk, Phase1/ 2 in HIV-1 infected pediatric subjects	TDF 75mg tablets, administered based on body weight (75, 150, 225, 300 mg/day) TDF naïve subjects: TDF monotherapy on Day 1, followed by ARV therapy including TDF starting on Day 3. TDF experienced patients, ARV therapy including TDF; all with food.	96 weeks	7 enrolled, 7 evaluable	HIV-1 infected subjects (4-17 years) with plasma HIV-1 RNA ≥ 10,000 cps/mL; failed 2 prior ARV regimens	Complete
PK, safety	GS-02-983 1 site (USA)	Assess TDF PK, safety after single dose	OL, single dose, single center, Phase 1 in HIV-infected pediatric subjects	TDF oral suspension (8mg/kg) with other ARVs and food	Single dose	12	HIV-1 infected children (aged 2-8 years)	Complete
Safety, effectiveness	IMPAACT P1053 4 sites (USA)	Compare tolerability and safety of dual PI-based HAART (Groups 1A and 1B) and multi-NRTI regimen (Group 2) Compare changes in CD4% as measure of long-term immunologic health on a salvage regimen from baseline to weeks 49 and 96 of treatment with dual-PI HAART based regimen versus a multi-NRTI ART regimen Compare changes in BMD from baseline to week 48 and 96 of a dual-PI based regimen without TDF or a multi-NRTI regimen containing TDF.	Open label comparison of dual PI based regimen and multi-NRTI ART-based regimen in treatment experienced children who have experienced virologic failure	1 enrolled in dual PI-HAART, 5 enrolled in multi-NRTI ART	Up to 96 weeks	1 enrolled in dual PI-HAART, 5 enrolled in multi-NRTI ART	Antiretroviral treatment experienced children aged (4- <21 years)	Terminated early

Source: Adapted from Applicant's Tabular Listing of All Clinical Studies

5.2 Review Strategy

The focus of the safety and efficacy review for this sNDA was Trial GS-US-104-0321. Four Phase 1 and 2 PK and safety studies were reviewed for additional evidence of appropriate PK and safety signals and are found in Section 5.3. The majority of the efficacy analyses were performed by Dr. Eric Frimpong, Biostatistical Reviewer, while the safety review was performed by Dr. Rebecca Levorson, Clinical Reviewer. The current sNDA is a partial submission of pediatric studies performed by the Applicant for pediatric exclusivity and includes one phase 3 clinical trial which is reviewed in full in sections 6 and 7.

5.3 Discussion of Individual Studies/Clinical Trials

Two phase 1 and two phase 2 studies were performed prior to the clinical trial (GS-US-104-0321) in order to obtain pharmacokinetic, safety, and antiviral activity data in pediatric subjects prior to initiation of the phase 3 clinical trial. These phase 1 and 2 studies provided important dosing and safety information especially in regards to bone safety in growing children. Each of these 4 initial studies will be briefly reviewed and pertinent conclusions highlighted.

GS-01-926: A Phase 1 study of tenofovir disoproxil fumarate (PMPA prodrug), a novel nucleotide analog reverse transcriptase inhibitor, in children with HIV infection

This open label 96 week trial focused on determining the PK, safety, and antiviral activity of TDF in HIV-infected, highly treatment experienced pediatric patients aged 4 to <18 years of age. This included a week-long period of subjects receiving TDF monotherapy (175 mg/m2 of body surface area once daily with food) and PK measurements during that time period. Then, the subjects had an optimized background regimen (OBR) added to the daily TDF therapy and these subjects were evaluated for efficacy and safety for a 96 week treatment period. Eighteen subjects were enrolled and received study drug.

Overall PK data showed that after a single dose of TDF, pediatric subjects had lower than target exposures based on adult exposure at 300 mg per day. However, at steady state and with other antiretrovirals including those known to increase tenofovir concentrations, exposures were consistent with those observed in adults receiving TDF 300 mg per day.

During treatment with TDF, subjects had decreases in mean (-1.63 $\log_{10}$ copies/mL) and median (-1.27 $\log_{10}$ copies/mL) plasma HIV-1 RNA concentrations from baseline to week 96 (primary endpoint). In two subjects on TDF monotherapy, a decrease from

baseline to day 7 HIV-1 RNA concentrations was at least 0.5 $\log_{10}$ copies/mL. Six of 18 subjects achieved an immunologic response (defined as an increase in CD4 cell count of 10% on two or more determinations at least 4 weeks apart, with a minimum increase of 50 cells).

Five of 14 subjects developed NRTI-associated resistance mutations during treatment with TDF. Two had presumed reemergence of archived mutant virus, including K65R in one subject. Four subjects developed additional thymidine analog mutations (TAMs) and one subject developed Q151M.

TDF's overall safety profile was similar to that observed in adults. It was given for a mean duration of 90.5 weeks in combination with other antiretroviral drugs in 18 subjects. One subject died of subarachnoid hemorrhage that was considered unlikely to be related to TDF. Nine subjects experienced 22 treatment-emergent SAEs with 2 being considered possibly or probably related to TDF: skeletal injury and nephrolithiasis (both in the same subject). Five subjects discontinued study due to AEs: 3 due to increased transaminases and 2 with decreased BMD. All events resolved with cessation of TDF.

The most frequent AEs reported were vomiting (10 subjects), abdominal pain (7 subjects), diarrhea (7 subjects), and pyrexia (7 subjects). Nine subjects experienced AEs that were considered possibly or probably related to TDF: 4 with transaminase elevation, 2 with decreased BMD, 1 with pancreatitis, 1 with arthralgia, and 1 with skeletal injury and nephrolithiasis.

The only renal AE considered possibly related to study drug was the 1 subject with nephrolithiasis. The patient had a negative rechallenge to the drug with over 6 months follow up.

Four subjects experienced bone-related AEs during the study: 1 hand fracture, 1 skeletal injury (described as an apophyseal bruise at the base of the right fifth metatarsal), 2 cases of decreased BMD. Four subjects had marked changes in lumbar spine BMD during the study (defined as confirmed >6% decrease from baseline of lumbar spine BMD). These reductions were noted at the 24 week time point and BMD did not progress throughout the remainder of the study. Reductions in BMD were not a result of poor growth since height z-scores were stable during the study.

GS-01-927 A Phase 1/2, open-label, dose-finding, multiple center study of the pharmacokinetics and safety of tenofovir disoproxil fumarate administered in combination with other antiretroviral agents as advanced therapy in HIV-1 infected children and adolescents (aged 4-17)

This open label 96 week trial focused on the pharmacokinetics and safety of TDF in highly treatment experienced HIV-1-infected children. Subjects who were naive to TDF

got a 2 day monotherapy regimen with TDF and had single-dose PK assessed. Both the TDF naïve and experienced subjects had 96 weeks of TDF and HAART. Multiple-dose PK analyses were performed on day 7 of therapy. Seven subjects (3 naïve and 4 TDF treatment experienced) were enrolled in the study. Dosing was based on weight bands that provided approximately 4.4mg/kg daily dose of TDF extrapolated from adult dosing of 300 mg daily. For steady-state PK evaluations, the median doses of TDF adjusted for body weight and BSA were 5.62 mg/kg (range 4.7 - 6.6 mg/kg) and 155.4 mg/m2 (range 145 – 191.7 mg/m2)

Overall PK data showed that after a single dose of TDF, pediatric subjects had lower than target exposures; however, at steady state and with other antiretrovirals, exposures were consistent with those observed in adults receiving TDF 300 mg per day.

Antiviral activity analysis revealed a decrease in plasma HIV-1 viral load but this decrease was not sustained over the entire course of the study.

TDF's safety profile revealed two probably related renal adverse events (probable tubulopathy and elevated B-2 microglobulin). The renal tubular disorder AE lead to discontinuation of the subject from the study and reportedly resolved after withdrawal of TDF. There were no deaths during the study. All subjects reported AEs with the most common being cough (3), vomiting (2), pyrexia (2), ear infection (2), and rash (2). No specific laboratory abnormalities were noted as new safety signals.

Bone specific monitoring was not part of the study protocol when the study was initiated, but a protocol amendment required BMD assessments via DEXA scan and subjects had BMD screening at 40-48 weeks and again every 12 weeks thereafter. No fractures were reported in this study.

Medical Officer Comment: No baseline BMD assessments were done in this study. It is known from the adult study and also found in the current phase 3 study that the most significant changes in BMD occur within 24-48 weeks of initiation of TDF therapy. Therefore, without a baseline evaluation, no conclusions can be made regarding BMD and TDF therapy in this phase 1 study.

GS-02-983: A Phase 1, open-labeled, single-dose, single center study of the pharmacokinetics of tenofovir disoproxil fumarate oral suspension administered in combination with other antiretroviral agents in HIV-1 infected children

In this study, HIV-1 infected children aged 2-8 years of age were given a single oral dose of TDF suspension of 8 mg/kg followed by a standardized meal. Subjects had blood and urine analyzed over the next 12-24 hours for pharmacokinetic measurements including AUC and C_{max}. Overall, the 8 mg/kg dose resulted in similar systemic

exposures compared to those in fed HIV infected adults administered the commercially available 300 mg tablet.

There were no adverse events during the study. There were few laboratory abnormalities between baseline and Day 2 including: 1 grade 2 alkaline phosphatase, 1 grade 2 lipase, and 1 grade 1 creatinine elevation with a decreased creatinine clearance of 75.78 mL/min.

Overall, this study provided useful PK and safety data in the 2-8 year old population in order to determine an appropriate dose of the oral suspension for younger children. Of note, palatability was not formally assessed in the study, but the Applicant reports that subjects uniformly found it extremely distasteful and development of this formulation was not continued.

IMPAACT P1053: A phase 2, randomized, open-label study to evaluate the safety and effectiveness of two antiretroviral therapeutic strategies: a dual PI-based HAART regimen versus a multi-NRTI ART regimen, in ART-experienced children and youth who have experienced virologic failure

This exploratory phase 2 study enrolled highly treatment experienced HIV-1 infected subjects >4 years to <21 years old into either a dual PI based HAART or multi-NRTI based regimen and planned to enroll 254 subjects. It enrolled only 6 subjects and was terminated early due to slow accrual of subjects. The primary endpoints were to compare tolerability, safety, and change in CD4% between the two types of regimens. An additional primary endpoint was the comparison of BMD between TDF-containing and non-TDF-containing regimens.

One subject enrolled in the dual PI-based HAART group and 5 subjects enrolled in the multi-NRTI ART group. As the study enrolled poorly and was terminated, very few observations can be made from this study. One subject (b) (6)) who received TDF had grade 1 creatinine elevation and was taken off the study. This same subject reported paresthesias and right knee pain. One subject had decreased neutrophil count and was on zidovudine at the time. One subject in the multi-NRTI group reported dyspnea. Few subjects completed the required BMD evaluations so no specific conclusions can be made regarding BMD and drug use in these subjects.

6 Review of Efficacy

Efficacy Summary

Study 0321 is the first phase 3 pediatric clinical trial in HIV-1 infected adolescents treated with TDF. It was designed to detect a treatment difference in HIV-1 RNA levels in highly-ARV experienced adolescent subjects aged 12- <18 years of age taking once

daily 300 mg tablet of TDF. It was a double-blind, placebo-controlled trial in which subjects failing their current antiretroviral therapy were randomized to a genotype-guided OBR and TDF or to a genotype-guided OBR and placebo. The primary efficacy endpoint was time-weighted average change from baseline to 24 weeks in HIV-1 RNA copies/mL ($DAVG_{24}$).

This trial failed to meet its primary efficacy endpoint of showing a statistically significant difference in HIV-1 RNA levels between TDF + OBR treated HIV-1 infected adolescents and placebo + OBR treated HIV-1 infected adolescents after 24 weeks of treatment. In post-hoc subgroup analyses, subjects with minimally efficacious OBR who were randomized to the TDF arm demonstrated a reduction in HIV-1 replication. This was a small subpopulation and not statistically significant.

Several factors contributed to this final efficacy outcome. At baseline, the study population was highly resistant to antiretroviral drugs as all of these subjects were perinatally infected with HIV-1 infection and had been on ARVs for many years. In addition, many of these subjects, despite being naïve to TDF therapy, had HIV-1 genotypes revealing mutations associated with resistance to TDF.

The choice of endpoint ($DAVG_{24}$) has been used in earlier HIV treatment trials but is currently not recommended as a primary efficacy endpoint by the Division of Antiviral Drug Products (DAVDP) as it appears to be a less sensitive analytic method than other analyses. However, when the Applicant was initially designing their pediatric clinical trials, the DAVP review team agreed to the $DAVG_{24}$ endpoint.

The study population was not appropriately sized to detect a treatment effect of a single ARV in a cohort of highly-ARV resistant subjects. A much larger study would have been required in pediatric subjects in order to power such a study.

Overall, the trial failed to show a difference in virologic response as measured by $DAVG_{24}$ between the TDF 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 TDF or OBR. Although changes in HIV-1 RNA in these highly treatment-experienced adolescent subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of TDF in patients $\geq$12 years of age who weigh $\geq$ 35 kg and whose HIV-1 isolate is expected to be sensitive to TDF.

6.1 Indication

The indication sought by the Applicant is for treatment of HIV-1 infection in adolescents aged 12 to <18 years of age.

6.1.1 Methods

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of TDF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents

The phase 3 study submitted for regulatory review is the 48 week interim analysis of the Applicant's on-going trial of TDF in highly antiretroviral experienced 12 -<18 year old HIV-1 infected subjects.

The primary objective of this study was to assess the efficacy of TDF plus a genotype-guided OBR compared to placebo plus OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL. The primary efficacy endpoint was time-weighted average change from baseline through Week 24 ($DAVG_{24}$) in plasma HIV-1 RNA. The secondary efficacy endpoints of this study were to evaluate the time-weighted average change from baseline through Week 48 ($DAVG_{48}$) in plasma HIV-1 RNA, to evaluate the proportion of patients achieving a HIV-1 RNA decrease of ≥ 1.0 $\log_{10}$ copies/mL at Weeks 24 and 48, and to assess the proportion of patients with HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Weeks 24 and 48.

The secondary objectives were to evaluate the safety and tolerability of TDF plus OBR compared to placebo plus OBR and to measure changes in BMD in the two treatment arms. Adverse events, clinical laboratory tests, and BMD measurements were assessed as measures of the safety of the drug.

The study planned to enroll 100 treatment-experienced HIV-1 infected adolescents (12 years to < 18 years) weighing ≥ 35 kg, who were failing their current antiretroviral regimen with HIV-1 RNA ≥ 5,000 copies/mL. The subjects were enrolled from 17 sites in Brazil and a single site in Panama.

Medical Officer Comment: The definition of failing current antiretroviral regimen was amended with the first protocol amendment to state that subjects with HIV-1 RNA ≥1,000 copies/mL would be enrolled. Lowering the entry criteria was reasonable as HIV-infected subjects taking HAART therapy should show evidence of effective therapy with HIV viral loads remaining below 1,000 copies/mL.

The trial fell short of its initial target enrollment with a total of 87 subjects.

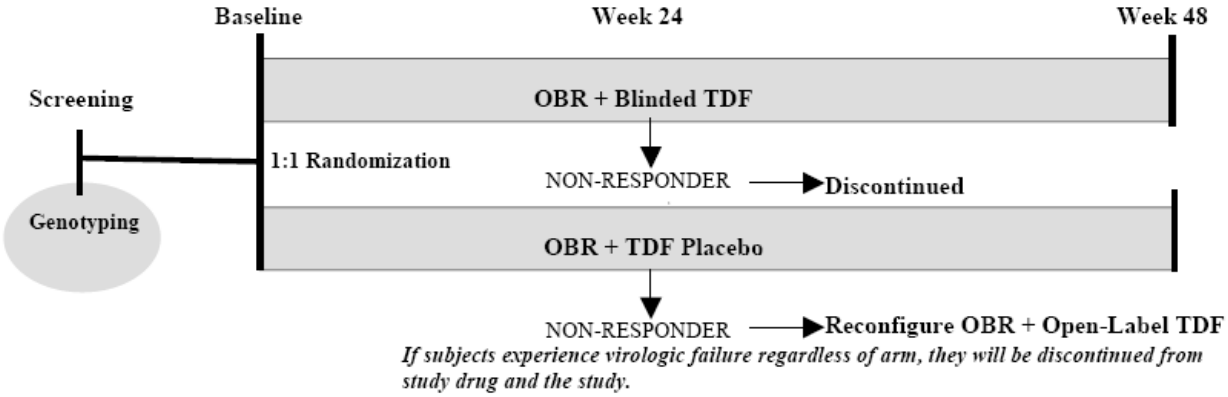
Pertinent criteria for inclusion and exclusion of subjects into this trial included the following:
1. Chronic HIV-1 infected patients
2. 12 years to < 18 years of age
3. Weight ≥ 35 kg

4. Able to swallow oral pills
5. Plasma HIV-1 RNA ≥ 1000 copies/mL
6. Prior antiretroviral treatment experience with at least 2 antiretroviral drug classes
7. Currently receiving combination antiretroviral therapy for at least 12 weeks
8. Naive to TDF
9. Absence of K65R mutation on genotypic testing
10. Adequate hematologic, renal and hepatic functions
11. Ability to construct an optimized background regimen, not containing didanosine, based on resistance testing
12. Absence of prior history of significant renal disease (i.e., nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis)
13. Absence of prior history of significant bone disease (i.e., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochondroses, multiple bone fractures)

Safety evaluations included physical examinations and laboratory analyses at screening, baseline, weeks 4, 8, 16, 24, 32, 40, and 48 and 30-day follow-up post early study drug discontinuation or study completion. Dual energy x-ray absorptiometry (DEXA) scans of the lumbar spine and whole body were performed at baseline, Week 24 and Week 48 to measure spine BMD, total BMD and total bone mineral content (BMC).

The following schema (Figure 1) presents the clinical study design of the trial.

Figure 1: Study Schema



Subjects were randomized in 1:1 ratio into two treatment arms. Arm 1 consisted of TDF plus a genotype specific OBR and Arm 2 consisted of placebo plus genotype specific OBR. HIV-1 genotyping was performed as part of the screening assessment in order to assist in the construction of an OBR. Prior to the baseline visit, patients who met entry criteria were randomized into a 1:1 ratio to receive either TDF plus OBR or placebo plus

OBR for 48 weeks. OBR was defined as at least 3 but no more than 5 antiretroviral agents not including TDF or placebo.

Subjects randomized to the TDF arm received one 300 mg TDF tablet daily in addition to OBR. Subjects randomized to the placebo arm took one TDF placebo tablet daily that was identical in appearance to the active TDF 300 mg tablet. Patients who meet the criteria for non-responder at Week 24 (defined as a decrease in HIV-1 RNA of < 0.5 $\log_{10}$ copies/mL from baseline) were unblinded. Patients randomized to the placebo arm were given the option to continue on-study and receive open-label TDF with an appropriate background regimen to be determined at the discretion of the investigator. Patients randomized to the TDF arm who meet the definition of nonresponder were discontinued from study and were instructed to discuss further treatment options with their physician.

Clinical Evaluations

Screening Visit
The following evaluations were to be completed at the screening visit: medical history including history of HIV-1 disease-related events, concomitant medications, and antiretroviral regimen, complete physical examination and baseline laboratory evaluations. Laboratory evaluations included complete blood counts, expanded chemistry profiles, urinalysis, HIV-1 genotyping, CD4 count and percent, and HIV-1 RNA quantification.

Baseline Visit
At the baseline visit, data were collected by interval history, physical examination, laboratory evaluations, and bone evaluations including DEXA and bone biochemical studies. OBR was constructed and study drugs were dispensed.

Week 4 to 48 Assessments
Every 4 weeks, subjects were evaluated by physical examination, review of AEs and changes in medications, and laboratory evaluations including bone biochemical studies.

Post-Treatment Assessments

Assessments for Premature Discontinuation from Study (Early Study Drug Discontinuation Visit) and 30 Day Follow-Up Visit
If the patient permanently discontinued study drug prior to Week 48, the patient was asked to return to the clinic within 72 hours of stopping study drug for an Early Study Drug Discontinuation Visit. All subjects were to have a 30 day follow-up visit after study completion.

The following assessments were performed at the early discontinuation visit and at the 30 day follow-up visit: complete physical examination, review of AEs and changes in

medications, laboratory evaluations including hematologies, chemistries, HIV RNA quantification, CD4 cell count and percentage.

Bone Mineral Density
Dual energy x-ray absorptiometry (DEXA) scans were performed at the Baseline Visit and at Weeks 24 and 48 using pediatric software approved by the DEXA vendor selected by Gilead. Scans were made of the spine and whole body to measure changes in BMD and bone mineral content. All DEXA scan results were provided to the study sites. A complete description of the procedures to be performed for the DEXA scans was provided by the DEXA vendor in a DEXA Procedural Manual.

Bone Biochemical Marker
Laboratory samples were taken at Baseline and at Weeks 4, 16, 24, 32, and 48 for measuring of bone biochemical markers. Patients were asked to report for each of these visits in the morning in a fasted state or, if fasting is not feasible, at the same time (±2 hours from the baseline draw time) at each subsequent visit. All samples were sent to a central laboratory in accordance with the Laboratory Procedural Manual. Analyses included measurement of N-telopeptide, C-telopeptide, osteocalcin, bone specific alkaline phosphatase, vitamin D (25-hydroxy), and parathyroid hormone. Bone biochemical marker results were not provided to the study sites.

Analysis Populations
Data for the first 48 weeks of the study were evaluated using the following analysis sets:

- **Randomized**: the randomized analysis set included subjects who were randomized into the study.

- **Randomized and Treated (RAT)**: the RAT analysis set included all subjects who were randomized into the study and received at least one dose of double-blind study medication. During the double-blind period of the study, data from subjects who received open-label TDF were excluded from the date the subject initiated open-label TDF onward. Data from subjects who received double-blind study medication other than their assigned treatment were to be analyzed according to the double-blind study medication received.

- **Intent-to-Treat (ITT)**: The ITT analysis set included all subjects who were randomized into the study and received at least one dose of study medication. Subjects with major eligibility violations (e.g., subject not of pediatric age, presence of the K65R mutation at screening, or prior experience with TDF identifiable based on pre-randomization characteristics) and subjects with plasma HIV-1 RNA < 1000 copies/mL at baseline were excluded. Data from subjects who received double-blind study medication other than their assigned treatment were to be analyzed according to the subject's assigned double-blind treatment group.

Data for subjects who switched to open-label TDF were excluded from the date the subject initiated open-label TDF onward.

- **Per Protocol (PP)**: The PP analysis set was to include subjects who received at least one dose of double-blind study drug, did not have any major eligibility violation at study entry, and did not commit any major protocol violations. Since only 1 additional subject (over those excluded from ITT) had a major protocol violation, no analyses were performed using the PP analysis set.

- **Pharmacokinetics (PK)**: The PK analysis set included all subjects who were enrolled in the pharmacokinetic substudy and for whom steady-state TDF pharmacokinetic parameters were evaluable.

The following three treatment groups were also defined:

- **Double-Blind TDF**: For ITT analyses, this group included subjects who were randomized to double-blind TDF. For RAT analyses, this group included subjects who were treated with double-blind TDF. Data collected after subjects initiated open-label TDF were excluded, with the exception of DEXA data, which were included up to 28 days after open-label dosing began.

- **Double-Blind Placebo (Placebo)**: For ITT analyses, this group included subjects who were randomized to double-blind placebo. For RAT analyses, this group included subjects who were treated with double-blind placebo. Data for subjects who switched to open-label TDF were excluded from the time of the subject's first dose of TDF, with the exception of DEXA data, which were included up to 28 days after dosing with open-label TDF began.

- **All TDF**: This group included double-blind phase and extension phase data for subjects who were initially randomized to double-blind TDF, or who were initially randomized to double-blind placebo and were later switched to open-label TDF. The latter subjects had their baseline reset and data from the date of the subject's first dose of TDF were included.

For FDA Analyses, an additional group of subjects was defined:

- **Placebo to Open-labeled TDF**: The placebo to open-labeled TDF group included RAT subjects who either had virologic failure at 24 weeks and were converted to open-labeled TDF or who completed 48 weeks of randomization on placebo and then were continued on open-labeled TDF.

6.1.2 Demographics

A total of 87 subjects were enrolled in this trial; 45 were randomized to the TDF arm and 42 to the placebo arm and received study drug. A total of 81 subjects continued on into the open-labeled All TDF arm after either 24 or 48 weeks of blinded treatment. All subjects were enrolled in Brazil and Panama and were Hispanic/Latino ethnicity. Refer to Table 3 for baseline and demographic characteristics.

There were slightly more females randomized to the placebo arm. There was relatively even distribution of races and ages between the groups. The mean weight and BMI in the placebo arm was higher than in the TDF arm. The baseline HIV-1 RNA levels, CD4 counts, and CD4 percentages were the same between treatment groups (Table 4).

Table 3: Demographics and Baseline Characteristics in the RAT population

Characteristic	**TDF** (N=45)	**Placebo** (N=42)	**Total** (N=87)	**All TDF** (N=81)
Sex				
Male	21 (47%)	17 (41%)	38 (44%)	35 (43%)
Female	24 (53%)	25 (60%)	49 (56%)	46 (57%)
Age (years)				
Mean (SD)	14 (1.5)	14 (1.5)	14 (1.5)	15 (1.4)
Min, Max	12, 17	12, 17	12, 17	12, 17
Race				
White	23 (51%)	22 (52%)	45 (52%)	43 (53%)
Black or African	14 (31%)	11 (26%)	25 (29%)	24 (30%)
Other	8 (18%)	9 (21%)	17 (20%)	14 (17%)
Weight (kg)				
Mean (SD)	45.8 (9.6)	49 (11.3)	47.4 (10.6)	48.4 (10.9)
Min, Max	35, 76.9	35, 82	35, 82	35, 91.1
Height (cm)				
Mean (SD)	155.8 (10.1)	156 (8.6)	155.9 (9.3)	156.9 (8.7)
Min, Max	138.5, 179.5	142, 179	138.5, 179.5	138.5, 179.5
Body Mass Index				
Mean (SD)	18.7 (2.3)	20 (3.2)	19.3 (2.8)	19.6 (3.2)
Min, Max	15.3, 26.9	15.4, 30.1	15.3, 30.1	14.4, 33.5

Source: Clinical Study Report (CSR) Table 6-4.

Table 4: Baseline Disease Characteristics in the RAT population

Baseline Disease Characteristics	**TDF** (N=45)	**Placebo** (N=42)	**Total** (N=87)	**All TDF** (N=81)
HIV-1 RNA (log_{10} cps/mL)				
Mean (SD)	4.7 (0.7)	4.6 (0.7)	4.6 (0.7)	4 (1.4)
Median	4.7	4.6	4.7	4.5
Q1, Q3	4.3, 5.3	4.2, 5	4.3, 5.1	3, 5
Min, Max	2.9, 6.4	2.2, 6.6	2.2, 6.6	1.7, 6.5
CD4 Cell Count (/mm3)				
Mean (SD)	390 (244)	357 (201)	374 (224)	422 (261)

Median	371	357	370	380
Q1, Q3	225, 543	258, 452	225, 483	228, 570
Min, Max	14, 893	43, 933	14, 933	14, 1164
CD4%				
Mean (SD)	17.8 (9.7)	17.6 (8.3)	17.7 (9)	19.4 (9.9)
Median	15	16.5	16	20
Q1, Q3	12, 25	11, 23	11, 24	12, 25
Min, Max	2, 43	2, 34	2, 43	2, 46

Source: CSR, table 6-5.

Genotype Susceptibility Score (GSS) was calculated for all subjects by summing up the scores of each ARV in the OBR at baseline using the ANRS (French National Agency for AIDS Research) algorithm. Post hoc analyses (after data finalization for the interim analysis) were also conducted using the genotypic resistance interpretation rules of the Stanford HIV database (HIV database program; http://hivdb.stanford.edu/index.html).

The ANRS algorithm uses a 3-point scale for GSS:
1.0 = absence of resistance
0.5 = possible resistance
0.0 = resistance

The Stanford HIV database program reports a GSS using a 5-point scoring system of sensitive, potential low-level resistance, low-level resistance, intermediate resistance, or high-level resistance for each drug. These data were converted into 5-point and 3-point numeric GSS scales for analysis, as follows:

Stanford 5-point scale for GSS:
1 = sensitive
0.75 = potential low-level resistance
0.5 = low-level resistance
0.25 = intermediate resistance
0 = high-level resistance

Stanford 3-point scale for GSS:
1 = sensitive or potential low-level resistance
0.5 = low-level resistance or intermediate resistance
0 = high-level resistance

Overall, 67% of subjects (64% in the TDF arm and 69% in the placebo arm) were prescribed 3 ARVs in addition to either TDF or placebo during the double-blind phase of this trial. Thirty-one percent in each were on 4 ARVs in addition to the study drug. Two subjects (4%) in the TDF arm were on 5 ARVs in addition to study drug (Table 5).

Baseline GSS revealed that a larger proportion of subjects in the TDF arm were more resistant to their OBR than in the placebo arm. Forty percent of TDF subjects had

baseline OBR GSS of ≤ 1; whereas, only 24% of placebo treated subjects had GSS ≤ 1 using the ANRS system (Table 6).

Table 5: Baseline ANRS OBR GSS and Number of ARVS in OBR at Baseline (RAT population)

Treatment Characteristics	**TDF** (N=45)	**Placebo** (N=42)	**Total** (N=87)
Number of ARVs in OBR			
3	29 (64%)	29 (69%)	58 (67%)
4	14 (31%)	13 (31%)	27 (31%)
5	2 (4%)	0	2 (2%)
GSS – OBR			
<= 1	18 (40%)	10 (24%)	28 (32%)
1.5	3 (7%)	2 (5%)	5 (6%)
2	10 (22%)	16 (38%)	26 (30%)
2.5	3 (7%)	2 (5%)	5 (6%)
>= 3	11 (24%)	12 (29%)	23 (26%)
GSS Stratum – OBR (2= median GSS)			
<= 2	31 (69%)	28 (67%)	59 (68%)
> 2	14 (31%)	14 (33%)	28 (32%)
Susceptibility for TDF			
0	1 (2%)	2 (5%)	3 (3%)
0.5	24 (53%)	15 (36%)	39 (45%)
1	20 (44%)	25 (60%)	45 (52%)

Source: CSR table 6-6.

Table 6: Baseline Stanford OBR GSS (RAT population)

Treatment Characteristics	**TDF** (N=45)	**Placebo** (N=42)	**Total** (N=87)
5 point GSS – OBR			
<= 1	15 (33%)	7 (17%)	22 (25%)
> 1	30 (67%)	35 (83%)	65 (75%)
p-value: TDF vs. Placebo	0.076		
<=2	33 (73%)	26 (62%)	59 (68%)
> 2	12 (27%)	16 (38%)	28 (32%)
p-value: TDF vs. Placebo	0.26		
3 point GSS – OBR			
<= 1	14 (31%)	6 (14%)	20 (23%)
> 1	31 (69%)	36 (86%)	67 (77%)
p-value: TDF vs. Placebo	0.064		
<= 2	32 (71%)	21 (50%)	53 (61%)
> 2	13 (29%)	21 (50%)	34 (39%)
p-value: TDF vs. Placebo	0.045		

Source: CSR table 6-7.

The baseline TDF susceptibility was 61% in the placebo group and 43% in the TDF group for the ITT analysis set. Patients with baseline TDF resistance in the placebo group had a higher virologic response measured as either HIV-1 RNA < 50 or < 400 at both weeks 24 and 48 compared to those in TDF group.

Adherence to study drug during the blinded period was similar between groups, but only 39% of subjects overall maintained ≥95% adherence to study drug (Table 7).

Table 7: Adherence to Randomized Study Drug During the Double-blind Treatment Period (RAT population)

Adherence to Randomized Study Drug (%)	**TDF** (N=45)	**Placebo** (N=42)	**Total** (N=87)
Mean (SD)	86% (15)	90% (12)	88% (14)
Median	93%	94%	94%
< 70%	5 (11%)	2 (5%)	7 (8%)
>= 70 - < 80%	5 (11%)	3 (7%)	8 (9%)
>= 80 - < 90%	10 (22%)	12 (29%)	22 (25%)
>= 90 - < 95%	8 (18%)	8 (19%)	16 (18%)
>= 95%	17 (38%)	17 (41%)	34 (39%)

Source: CSR Table 6-10.

6.1.3 Subject Disposition

One hundred twenty-three subjects were screened, 90 were randomized at 17 sites in Brazil (n=86) and 1 site in Panama (n=4). Forty-six subjects were randomized to the TDF arm and 44 to the placebo arm. Of those, 3 subjects (1 TDF, 2 placebo) were never treated with study medication. Eighty-seven subjects received at least one dose of study medication and comprised the RAT analysis set (45 TDF and 42 placebo). Two subjects (1 in each arm) had baseline HIV-1 RNA values <1000 copies/mL and were excluded from the ITT analysis set. The 85 remaining subjects made up the ITT population.

Medical Officer Comment: The two subjects who were excluded from the ITT population due to viral loads < 1000 copies/mL at baseline both had viral loads above 1000 copies/mL at their screening visits. Subject (b) (6) *randomized to the TDF arm had a viral load of 12,503 copies/mL at screening; however, at the baseline visit, viral load fell to 760 copies/mL. Subject* (b) (6) *randomized to the placebo arm had a viral load of 22,310 copies/mL at screening visit but dropped to 168 copies/mL at the baseline visit. The Applicant utilized the RAT population for its safety analyses and used the ITT populations (excluding these two subjects who did not meet enrollment criteria) for its efficacy analyses. The chosen populations for the different types of analyses appear appropriate.*

Of the 87 randomized and treated subjects, 56 completed the 48 week double-blind treatment period (27 subjects [60%] in the TDF group and 29 subjects [69%] in the placebo group). Subject disposition is summarized in Table 8.

In the TDF group, 18 subjects (40%) discontinued from the randomized phase of the study. In the placebo group, 13 subjects (31%) discontinued from the randomized phase and 3 discontinued from the study altogether. The most common reasons for discontinuation was unblinding at 24 weeks for virologic failure (14 subjects in the TDF arm and 11 subjects in the placebo arm). Ten subjects unblinded for virologic failure in the placebo arm were enrolled in the open-label extension phase of the trial. Two subjects in each group discontinued due to investigator discretion. Two subjects in the TDF group discontinued due to safety/tolerability/efficacy reasons (one due to vomiting as AE and one due to intolerance to ARV regimen).

Sixty subjects received TDF in an open-labeled extension phase (24 who were originally randomized to TDF arm and 36 who were initially randomized to placebo). In the TDF arm, 24 of 27 subjects who completed the 48 week randomized phase enrolled in the open-labeled extension phase. In the placebo group, in addition to the 10 of 11 who were discontinued at 24 weeks due to virologic failure, 26 of the 29 subjects who completed the randomized phase enrolled in the open-labeled extension phase.

Medical Officer Comment: There was a large proportion of subjects in both arms (40% in TDF and 31% in placebo) who were discontinued early from the randomization phase. Most of these subjects were discontinued due to virologic failure.

Table 8: Disposition of Study Subjects (All subjects)

	TDF	Placebo	Total
Number of subjects screened			123
Number of screen failures			33
Subjects Randomized	46	44	90
Subjects Randomized and Not Treated	1	2	3
Withdrew Consent	1	2	3
Subjects Randomized and Treated (RAT)	45	42	87
Subjects Completing 48 week Randomized Phase	27 (60%)	29 (69%)	56 (64%)
Subjects Early Discontinued from Randomization Phase	18 (40%)	13 (31%)	31 (36%)
Reasons for Discontinuation in Randomization Phase			
Virologic Failure	14 (31%)	11 (26%)	25 (29%)
No Virologic Data **Reasons**			
Discontinued Study due to AE/Death	1 (2%)	0	1 (1%)
Discontinued Study for Other Reasons[a]	3 (7%)	2 (5%)	5 (6%)
Missing Data but Still in Study	0	0	0
Subjects Treated in Extension Phase	24	36	60
Subjects Ongoing in Extension Phase	16 (67%)	25 (69%)	41 (68%)
Subjects Early Discontinued from Extension Phase	8 (33%)	11 (31%)	19 (32%)
Discontinuation due to Investigator's Discretion	7 (29%)	7 (19%)	14 (23%)
Discontinuation due to Safety, Tolerability, or Efficacy Reasons	1 (4%)	4 (11%)	5 (8%)

[A]: Includes investigator discretion, withdrew consent.
Source: Adapted from CSR Table 6-2.

Table 9 provides the total number of subjects in each analysis set.

Table 9: Analysis Sets

Analysis Set	TDF (N=45)	Placebo (N=42)	Total (N=87)	All TDF (N=81)
RAT	45	42	87	81
ITT	44	41	85	79
PK	1	7	8	8

Source: CSR Table 6-11.

6.1.4 Analysis of Primary Endpoint

All subjects who were randomized, received at least one dose of study drug, and had no major eligibility violations were considered the ITT population and were included in the efficacy analyses. The primary efficacy endpoint was time-weighted average change from baseline through week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log_{10} copies/mL).

The Applicant reported that this trial did not show a statistically significant difference between treatment groups in $DAVG_{24}$. A median decrease of 1.58 log_{10} copies/mL in

the TDF group versus 1.55 log_{10} copies/mL in the placebo group was observed, resulting in a p-value of 0.55 (Table 10).

Table 10: Applicant's Table of Time-weighted Average Change in HIV-1 RNA from Baseline through Week 24 ($DAVG_{24}$) (ITT population)

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a,b,c]	**TDF (N = 44)**	**Placebo (N = 41)**	**p-value[d]**
DAVG Through Week 24			
N	44	41	
Mean (SD)	-1.25 (1.12)	-1.35 (1.25)	0.55
Median	-1.58	-1.55	
Q1, Q3	-2.15, -0.27	-2.36, -0.34	
Min, Max	-2.81, 0.89	-3.09, 0.88	

Source: CSR Table 7.1

FDA Statistical Reviewer, Dr. Eric Frimpong performed additional statistical analyses to further evaluate the primary and secondary efficacy endpoints. Please refer to his review for a complete statistical review of this submission.

Evaluations of virologic success as measured by HIV-1 RNA copies ≤ 400 copies/mL or ≤ 50 copies/mL at week 24 were performed (Tables 11 and 12). The same proportion of subjects in the placebo arm had virologic success (as defined by ≤ 400 copies/mL at 24 weeks) as did those in the TDF arm (41% in each arm). However, more placebo treated subjects had viral loads ≤ 50 copies/mL at 24 weeks (37% in placebo group compared to 20% in the TDF group).

Table 11: FDA Statistical Reviewer's Results - Virologic Outcome for HIV-1 RNA < 400 copies/mL at Week 24 (ITT Analysis Set)

	Tenofovir DF (N= 44)	**Placebo (N = 41)**
Virologic Success HIV RNA < 400 copies/mL	18 (41%)	17 (41%)
Virologic Failure	25 (57%)	24 (59%)
No Virologic Data at Week 24 Window		
Reasons		
Discontinued study due to AE or Death*	1 (2%)	0
Discontinued study for Other Reasons**	0	0
Missing data during window but on study	0	0

*Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
**Other includes: withdrew consent, loss to follow-up, moved etc.

Table 12: FDA Statistical Reviewer Results - Virologic Outcome for HIV-1 RNA < 50 copies/mL at Week 24 (ITT Analysis Set)

	Tenofovir DF (N= 44)	**Placebo (N = 41)**
Virologic Success HIV RNA < 50 copies/mL	9 (20%)	14 (34%)
Virologic Failure	34 (77%)	27 (66%)
No Virologic Data at Week 24 Window		
Reasons		
Discontinued study due to AE or Death*	1 (2%)	0
Discontinued study for Other Reasons**	0	0
Missing data during window but on study	0	0

*Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
**Other includes: withdrew consent, loss to follow-up, moved etc.

Subgroup Analyses of GSS and Primary Efficacy Endpoint

The Applicant performed subgroup analyses of subjects with baseline GSS ≤ 1 and > 1 to explore the contribution of TDF compared to placebo in an otherwise suboptimal regimen (see Tables 13 and 14). The Applicant had used the ANRS grading system initially in the trial, but also used the Stanford 3 and 5 point GSS grading systems in their post-hoc analyses. The Applicant concluded that in subjects with a Stanford OBR GSS ≤1, the difference in median $DAVG_{24}$ in plasma HIV-1 RNA between groups (TDF minus placebo) was -1.24 log_{10} copies/mL using the 5 point scale and -1.44 log_{10} copies/mL using the 3-point scale.

Medical Officer Comment: Post-hoc analyses are considered exploratory analyses. They can stimulate future study hypotheses; however, they provide limited additional data on which to substantiate claims from the current trial.

Table 13: Applicant's Results for Primary Efficacy Endpoint - Subjects with a Baseline ANRS OBR GSS ≤ 1 or > 1 log_{10} copies/mL (ITT Analysis Set)

	OBR GSS ≤ 1		**OBR GSS > 1**	
Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)	**TDF (N = 18)**	**Placebo (N =10)**	**TDF (N = 26)**	**Placebo (N = 31)**
N	18	10	26	31
Mean (SD)	-1.31 (1.09)	-0.89 (1.27)	-1.20 (1.15)	-1.49 (1.22)
Median	-1.66	-1.14	-1.47	-1.68
Q1, Q3	-2.00, -0.76	-2.23, 0.09	-2.19, -0.18	-2.48, -0.49
Min, Max	-2.75, 0.61	-2.41, 0.88	-2.81, 0.89	-3.09, 0.77
p-value: TDF vs. Placebo	0.40		0.33	

Source: CSR table 7-2.

Table 14: Applicant's Post-Hoc Subgroup Analyses of $DAVG_{24}$ stratified by GSS Stanford Scale

Time-Weighted Average Change in HIV-1 RNA (Log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)	**OBR GSS ≤ 1**		**OBR GSS > 1**	
	TDF	**Placebo**	**TDF**	**Placebo**
5-point GSS OBR DAVG Through Week 24				
N	15	7	29	34
Mean (SD)	–1.12 (1.18)	–0.39 (1.17)	–1.31 (1.1)	–1.54 (1.18)
Median	–1.21	0.04	–1.64	–1.72
Q1, Q3	–2.00, 0.07	–1.22, 0.81	–2.19, –0.60	–2.43, –0.72
Min, Max	–2.75, 0.89	–2.29, 0.88	–2.81, 0.71	–3.09, 0.77
p-value: TDF vs. Placebo	0.26		0.40	
3-point GSS OBR DAVG Through Week 24				
N	14	6	30	35
Mean (SD)	–1.17 (1.21)	–0.28 (1.24)	–1.28 (1.09)	–1.53 (1.17)
Median	–1.38	0.06	–1.62	–1.68
Q1, Q3	–2.00, 0.07	–1.22, 0.81	–2.19, –0.36	–2.43, –0.72
Min, Max	–2.75, 0.89	–2.29, 0.88	–2.81, 0.71	–3.09, 0.77
p-value: TDF vs. Placebo	0.23		0.37	

Source: CSR Table 7-3.

TDF Resistance

Virologic success was evaluated by HIV-1 RNA < 400 copies/mL and < 50 copies/mL in subjects with baseline susceptibility or resistance to TDF by treatment arm (Tables 15 and 16). Subjects with HIV baseline susceptible to TDF (GSS =1) were more likely to have virologic success at 24 weeks, though not statistically significant.

An exploratory analysis was performed to evaluate the number of subjects per arm who had low baseline OBR GSS and also were sensitive to TDF at baseline. There were only 3 subjects in each arm who had OBR GSS ≤ 1 and were also sensitive to TDF at

baseline. No interpretation of statistical analyses could be rendered due to the small sample size.

Table 15: FDA Statistical Reviewer's Analysis - Number and Percentage of Subjects with Plasma HIV-1 RNA < 400 copies/mL in Subjects with a Baseline TDF GSS < 1 or = 1 (M=F; ITT set)

	TDF Resistance, GSS < 1		**TDF Susceptible, GSS = 1**	
	TDF (N = 25)	**Placebo (N = 16)**	**TDF (N = 19)**	**Placebo (N = 25)**
At Week 24 (M=F)	12 (48%)	11 (69%)	6 (32%)	6 (24%)
p-value	0.22		0.74	
At Week 24 (ITT set)	9 (36%)	11 (69%)	6 (32%)	7 (28%)
p-value	0.06		1.00	

Table 16: FDA Statistical Reviewer's Analysis - Number and Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL in Subjects with a Baseline TDF GSS < 1 or = 1 (M=F; ITT set)

	TDF Resistance, GSS < 1		**TDF Susceptible, GSS = 1**	
	TDF (N = 25)	**Placebo (N = 16)**	**TDF (N = 19)**	**Placebo (N = 25)**
At Week 24 (M=F)	6 (24%)	10 (63%)	6 (32%)	6 (24%)
p-value	0.02		1.00	
At Week 24 (ITT set)	7 (28%)	10 (63%)	5 (26%)	5 (20%)
p-value	0.05		0.72	

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints included $DAVG_{48}$, the median change in HIV-1 RNA at week 48 (with the last observation carried forward [LOCF]), proportion of subjects with HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Week 48, and time to virologic failure by Week 48. See Tables 17, 18, and 19 for these details. Additional analyses included CD4 cell count, percentage, and emergence of resistance mutations over course of treatment.

Overall, the secondary efficacy endpoints did not produce statistically significant differences between TDF and placebo treatment groups.

Table 17: Time-weighted change from baseline in plasma HIV-1 RNA through Week 48 ($DAVG_{48}$) in the ITT population

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 48 ($DAVG_{48}$)	**TDF (N = 44)**	**Placebo (N = 41)**	**p-value[d]**
DAVG Through Week 48			
N	44	41	0.40
Mean (SD)	–1.28 (1.19)	–1.46 (1.24)	
Median	–1.42	–1.35	
Q1, Q3	–2.25, –0.25	–2.72, –0.53	
Min, Max	–3.14, 0.83	–3.14, 0.87	

Source: CSR Table 7-4.

The proportion of subjects with plasma HIV-1 RNA < 400 copies/mL at week 48 was 34% (15/44) in the TDF group and 46% (19/41) in the placebo group (Table 18). The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at week 48 was 27% (12/44) in the TDF group and 39% (16/41) in the placebo group (Table 19).

Table 18: FDA Statistical Reviewer's Results - Virologic Outcome for HIV-1 RNA < 400 copies/mL at Week 48 (ITT Analysis Set)

	Tenofovir DF (N= 44)	**Placebo (N = 41)**
Virologic Success HIV RNA < 400 copies/mL	15 (34%)	19 (46%)
Virologic Failure	27 (61%)	21 (51%)
No Virologic Data at Week 48 Window		
Reasons		
Discontinued study due to AE or Death*	1 (2%)	0
Discontinued study for Other Reasons**	1 (2%)	1 (2%)
Missing data during window but on study	0	0

*Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
**Other includes: withdrew consent, loss to follow-up, moved etc.

Table 19: FDA Statistical Reviewer's Results - Virologic Outcome for HIV-1 RNA < 50 copies/mL at Week 48 (ITT Analysis Set)

	Tenofovir DF (N= 44)	**Placebo (N = 41)**
Virologic Success HIV RNA < 50 copies/mL	12 (27%)	16 (39%)
Virologic Failure	30 (68%)	24 (59%)
No Virologic Data at Week 48 Window		
Reasons		
Discontinued study due to AE or Death*	1 (2%)	0
Discontinued study for Other Reasons**	1 (2%)	1 (2%)
Missing data during window but on study	0	0

*Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
**Other includes: withdrew consent, loss to follow-up, moved etc.

Secondary Efficacy Analysis Based on GSS

Post-hoc analyses were performed in order to assess the effect of baseline GSS on the secondary efficacy endpoints at 48 weeks. Treatment groups were divided by GSS scores $\leq$ 1 or >1 for each efficacy measure. In subjects with the highest baseline resistance to their treatment regimen (GSS $\leq$ 1), the decreases in HIV-1 RNA were larger in the TDF arm than in the placebo arm. The median reduction of HIV-1 RNA was -1.5 $\log_{10}$ copies/mL for the TDF arm compared to -0.93 $\log_{10}$ copies/mL for the placebo arm (p value of 0.49). See Table 20 for details.

Table 20: Time-weighted change from baseline in plasma HIV-1 RNA through Week 48 ($DAVG_{48}$) in subjects with a baseline ANRS OBR GSS < 1 or > 1 $\log_{10}$ copies/mL in the ITT population

Time-Weighted Average Change in HIV-1 RNA (Log_{10} copies/mL) from Baseline through Week 48 ($DAVG_{48}$)	**OBR GSS $\leq$ 1**		**OBR GSS > 1**	
	TDF (N = 18)	**Placebo (N = 10)**	**TDF (N = 26)**	**Placebo (N = 31)**
DAVG Through Week 48				
N	18	10	26	31
Mean (SD)	–1.36 (1.2)	–0.94 (1.37)	–1.22 (1.20)	–1.63 (1.17)
Median	–1.5	–0.93	–1.32	–1.58
Q1, Q3	–2.36, –0.62	–2.44, 0.07	–2.18, –0.08	–2.76, –0.72
Min, Max	–2.90, 0.76	–2.82, 0.87	–3.14, 0.83	–3.14, 0.68
p-valued: TDF vs. Placebo	0.49		0.17	

Source: CSR table 7-5.

Other Secondary Endpoints

In other secondary endpoints, no significant differences were found. There was no significant difference between the two treatment groups in time to virologic failure by 48 weeks or in CD4 cell count or percentage from baseline through 48 weeks

Virologic Resistance

Baseline genotyping was performed at screening. Post-baseline HIV genotypes were performed on subjects who had virologic failure or had HIV-1 viral load ≥400 copies/mL at weeks 24, 48, 96, early discontinuation, or their last available plasma sample prior to week 48 analysis data cutoff dates.

Baseline genotype results revealed that the study population had extensive prior antiretroviral therapy. Ninety percent of subjects had HIV virus that contained one or more NRTI-associated resistance mutations (NAMs) with the mean number of NAMs being 4.8 and 3.9 per subject in TDF and placebo arms, respectively. Eighty percent of subjects had thymidine-analog mutations (TAMs) at screening (mean 3 and 2.2 TAMs in the TDF and placebo groups, respectively). Additionally, 53% subjects had NNRTI-resistance mutations and 61% contained major protease resistance mutations.

Forty-six of the 87 subjects had post-baseline genotypes performed (29 subjects from the TDF arm and 17 subjects from the placebo arm). For the TDF treated subjects, the genotype could have occurred during the blinded or open-labeled portion of the trial; whereas, for the placebo subjects, genotyping occurred only during the double-blind phase of the trial. The length of drug exposure and the length of time in which to develop resistance mutations were not equal between the two groups as subjects randomized to the TDF arm could be assessed both in the double blind and also open-labeled portion of the trial. Mean time from baseline to analysis was 345 days for the TDF group vs. 275 days for the placebo group.

NAMs developed in 24% of the assayed subjects (9 TDF subjects and 2 placebo subjects). One subject developed K65R mutation in the TDF arm. See Table 21 for details.

Table 21: Development of HIV-1 Resistance Mutations

	Tenofovir DF			Placebo		
	N	% Total (n = 45)	% RAP[a] (n = 29)	N	% Total (n = 42)	% RAP (n = 17)
Any NAM[b]	9	20%	31%	2	5%	12%
K65R	1	2%	3%	0	0%	0%
M184V/I	4	9%	14%	2	5%	12%
Any TAM[c]	4	9%	14%	1	12%	6%
NNRTI-R[d]	9	20%	31%	3	7%	18%
Primary PI-R[e]	6	13%	21%	2	5%	12%
Secondary PI-R[f]	9	20%	31%	7	17%	41%
No mutation development[g]	10	22%	34%	10	24%	59%

Source: CSR Table 7-17.

For further details on viral resistance mutations please refer to Dr. Narayana Battula's Virology Review.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The small trial size did not allow for meaningful subgroup analysis of efficacy by gender or race. See section 6.1.5 for more details on other subpopulations..

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Pharmacokinetic evaluations of TDF were performed in 8 trial subjects at steady-state during the open-labeled portion of the trial. Adolescent subjects had similar TDF exposures as compared to previous studies in HIV-1 infected adults (Table 22).

Table 22: Summary of Steady-state Pharmacokinetic Parameters for TDF (PK analysis set)

TFV Plasma PK Parameter (Units)	GS-US-104-0321[a] 300 mg/day (N = 8)	GS-97-901[b] 300 mg/day		GS-99-907[b] 300 mg/day			
		8th Dose (N = 8)	28th Dose (N = 8)	12 Weeks (N = 12)	24 Weeks (N = 12)	36 Weeks (N = 7)	48 Weeks (N = 7)
AUC_{tau} (ng•h/mL)[c] Mean (% CV)	3390.6 (36.0)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
$AUC_{0\text{-last}}$ (ng•h/mL) Mean (%CV)	2256.4 (32.7)	—	—	—	—	—	—
C_{max} (ng/mL) Mean (%CV)	377.5 (35.6)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{last} (ng/mL) Mean (%CV)	133.4 (42.6)	—	—	—	—	—	—
C_{tau} (ng/mL)[c] Mean (%CV)	64.4 (52.6)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.98 (1.46, 2.99)	3.0	2.3	2.3	2.3	1.5	2.5
T_{last} (h) Median (Q1, Q3)	12.00 (11.96, 12.00)	—	—	—	—	—	—
$T_{½}$ (h)[c] Median (Q1, Q3)	10.54 (9.02, 15.30)	13.7	14.4	14.0	14.9	12.4	14.5

a Measured after a minimum of 4 weeks of treatment with tenofovir DF.
b Historical data in HIV-1 infected adults.
c Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour time point.

Source: CSR, Table 8-1.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.5 for Virologic Resistance and the Clinical Virology Review for further details.

6.1.10 Additional Efficacy Issues/Analyses

HIV-1 viral load is a validated primary efficacy endpoint for treatment of HIV-1 infection. There are several methods to evaluate HIV-1 viral load. DAVG is an older method, no longer the most commonly measured endpoint of efficacy in HIV-1 infection. Currently there are other methods that are more commonly accepted in HIV-1 drug trials.

Assessment of viral load at 24 weeks is also no longer the most commonly accepted primary efficacy time point for standard evaluation of drugs in treatment naïve patients. Viral load measurement at 48 weeks provides a longer treatment period in order to assess overall drug effect. However, when the pediatric trials were being designed, these were acceptable measures for a primary efficacy endpoint and were agreed upon by the Applicant and the agency.

This clinical trial as designed failed to show that the addition of TDF to an optimized background regimen of other active antiretroviral agents was more effective at reducing HIV-1 viral load than placebo plus OBR in a highly antiretroviral drug experienced adolescent HIV population. The subject population was not an ideal population to study, as it turned out; subjects were highly drug resistant at baseline and had few fully active drugs available. The sample size was not large enough to demonstrate a treatment difference between the two groups as the study was underpowered. In addition, non-adherence to treatment and development of resistance is well known in the adolescent population and could have been an additional factor leading to failure to show a treatment difference.

Post-hoc subgroup analyses of the subjects with most OBR resistance provide some evidence of the activity of TDF. In addition, the steady-state PK study performed provides solid evidence of appropriate exposures compared to the adult PK data.

7 Review of Safety

Safety Summary

Overall, the safety issues identified in the adolescent study are similar to those previously identified in the adult clinical trials and are included in the current product label. Specific safety concerns related to TDF include loss of BMD, renal toxicity, and gastrointestinal side effects.

Loss of BMD and biochemical evidence of increased bone turnover were observed more in the TDF treated adolescent subjects than in the placebo treated subjects. These effects did not reach statistical significance, but the trial was not powered for this endpoint. Subjects had evidence of loss of BMD at 24 to 48 weeks as was observed in the adult trial. The degree of BMD loss was not significantly more in the adolescent subjects than in the adult subjects; however, adolescence is a time period of rapid gain of BMD. It is unclear what the long term effects of TDF will be in subjects who were exposed to it during adolescence.

Renal toxicity including proximal tubular defects is known to be associated with TDF. In this trial, no subject had evidence of Fanconi's syndrome; however, complete evaluations for Fanconi's syndrome were not required in the trial. No subjects

developed renal failure attributable to study drug. Overall, the trial provided no evidence of new renal events to monitor.

Gastrointestinal events including abdominal pain, nausea, gastritis (dyspepsia), vomiting, and diarrhea were observed in the adolescent trial as were seen in the adult trials. Increased rates of abdominal pain and vomiting were noted in the adolescents compared to the adults in the clinical trials.

The most outstanding safety concerns include being better able to predict who will develop renal and BMD AEs and further elucidating the underlying mechanism behind these AEs in order to offer better monitoring for these AEs, adjunctive care, or avoidance of TDF in patients at high risk of renal or bone AEs. In addition, continued surveillance of subjects who have been exposed to TDF during childhood will be beneficial in regards to predicting its long term effects on BMD when administered during a period of intense bone maturation.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A single double-blind placebo controlled clinical trial of highly treatment experienced adolescent HIV-1 infected subjects was used to evaluate the safety of TDF. Safety evaluations of the previous phase 1 and 2 pediatric trials are included in section 5.1.

In Study 321, all subjects who were randomized and received at least one dose of test drug are included in the safety analyses. These subjects comprise the RAT population (Table 23).

Table 23: Subjects included in the RAT population

TDF (double blind)	**Placebo** (double blind)	**All TDF** (open label)	**Placebo to Open-label TDF**
45	42	81	36

7.1.2 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary version 11.1. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms that were reviewed by this FDA clinical reviewer.

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

This single phase 3 study was utilized for the safety analyses in this review.

7.2 Adequacy of Safety Assessments

Safety evaluations were performed based on the known safety signals observed in the adult clinical trials and the phase 1 and phase 2 pediatric trials. Special monitoring of renal, gastrointestinal, bone, and growth parameters was performed in this trial.

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

56 subjects (64%) were exposed to study drug for a minimum of 48 weeks during the randomization phase. Subjects randomized to the placebo arm were allowed to be continued on an open-labeled extension phase with TDF if they had evidence of virologic failure at 24 weeks of therapy. Overall, 60 subjects (69% of RAT population) continued in the open-labeled TDF extension phase. Twenty-eight subjects (32% of RAT population) continued in the open-labeled extension phase at 96 weeks of therapy. All subjects received the approved dose of TDF (300 mg tablet once daily). The pharmacokinetic substudy provided evidence of appropriate target exposure with this dosing. As previously noted, all subjects were from Brazil and Panama with a relatively even distribution of male and female adolescent subjects.

As this trial had a double-blind part and an open-labeled part to it, the subjects who were randomized to TDF and completed the first 48 weeks of therapy were exposed to TDF longer than the subjects who were exposed to placebo for 24 weeks and had evidence of virologic failure at 24 weeks. Therefore, treatment groups are broken down into **TDF treated** subjects which pools all subjects who were randomized to the TDF arm and completed some time on TDF. These subjects could have completed a time course less than 24 weeks, completed 24 weeks and been discontinued for virologic failure, completed 48 weeks and either decided to continue in open labeled TDF or not to continue TDF.

The **placebo** group included those subjects who were randomized to the placebo arm of the trial. This included subjects who completed a time course less than 24 weeks, completed 24 weeks and discontinued due to virologic failure, or continued to 48 weeks on placebo therapy.

The **placebo to open-labeled TDF** group included subjects who either had virologic failure at 24 weeks and were converted to open-labeled TDF or who completed 48 weeks of randomization on placebo and then were continued on open-labeled TDF.

7.2.2 Explorations for Dose Response

Please refer to review by Dr. Shirley Lu, Clinical Pharmacologist for details.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Subjects had baseline and routine laboratory and radiologic evaluations for adverse events in addition to focused physical examinations at follow up visits. Please refer to section 6.1.1 Methods for detailed information in regards to clinical testing.

At the screening visit subjects had serum pregnancy test (post-menarchal females only), hematology profile (complete blood count [CBC] with differential and platelet count), chemistry profile: albumin, alkaline phosphatase, AST, ALT, total bilirubin, bicarbonate, BUN, calcium, chloride, cholesterol, CK, creatinine, glucose, magnesium, phosphorus, potassium, sodium, triglycerides, uric acid, and amylase (reflex pancreatic lipase testing was performed on samples with total amylase ≥ 1.5 × ULN), estimated Glomerular Filtration Rate (GFR) using the Schwartz Formula, and urinalysis performed.

At the baseline and follow-up visits, subjects had serum pregnancy test, hematology profile, chemistry profile, urinanalysis, and bone evaluations performed.

Subjects had baseline and interval evaluations of BMD including DEXA scans (weeks 24, 48) and analyses of bone biochemical markers (Weeks 4, 16, 24, 32, and 48) including N-telopeptide, C-telopeptide, osteocalcin, bone specific alkaline phosphatase, vitamin D (25-hydroxy), and parathyroid hormone.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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

As TDF is already approved in the US for treatment of HIV-1 infection in adults, evaluation of known adverse events were included in the current pediatric trial.

7.3 Major Safety Results

7.3.1 Deaths

There have been no deaths during the study.

7.3.2 Nonfatal Serious Adverse Events

More SAEs were reported in the TDF group than in the placebo treatment group (Table 24). None of the SAEs were considered related to the study drug by the investigators. On review of the SAE narratives, this FDA clinical reviewer agrees that the SAEs did not appear to be an adverse reaction to TDF but appeared related to the subjects' underlying HIV-1 infection. Pneumonia was the most common SAE in all groups. Subjects who were diagnosed with "*Pneumocystis jiroveci* pneumonia" were also diagnosed with "pneumonia" for the same event.

Medical Officer Comment: The two subjects in the TDF arm who developed pneumonia and Pneumocystis jiroveci pneumonia (PJP) were treated for both bacterial pneumonia and PJP as a definitive diagnosis could not be made. For each subject, this SAE was considered a single event.

Table 24: Serious Adverse Events in RAT population

TDF N=45	**Placebo** N=42	**Placebo to TDF (Open Labeled)** N=36
13 Events (29%)	4 events (10%)	8 events (22%)
Pneumonia and *Pneumocystis jiroveci* pneumonia 2 events (4%)	Pneumonia (2%)	Pneumonia (2) (6%)
Pneumonia (2%)	Mastoiditis (2%)	Herpes Zoster (2) (6%)
Sinusitis 2 events (4%)	Cerebral Toxoplasmosis (2%)	Abscess (3%)
Respiratory Tract Infection (2%)	Cellulitis (2%)	Limb abscess (3%)
Anal Abscess (2%)		Neurocryptococcosis (3%)
Cryptococcus (2%)		Psychotic disorder (3%)
Gastroenteritis 2 events (4%)		
Urinary Tract Infection (2%)		
Proteinuria (2%)		
Convulsions (2%)		

Source: FDA analysis of Applicant AE datasets

7.3.3 Dropouts and/or Discontinuations

One subject, Subject (b) (6), discontinued the trial due to an AE. She was a 14 year old white female randomized to the TDF arm who developed Grade 2 vomiting after the first administration of TDF. She continued to have vomiting that resolved on the day the last dose of TDF was taken.

Medical Officer Comment: Vomiting is a labeled AE of TDF. This subject dropout appears to be due to a drug related AE as vomiting resolved with discontinuation of TDF.

7.3.4 Significant Adverse Events

Treatment Emergent Treatment Related Adverse Events

The AE profile observed in this adolescent trial is similar to the profile observed in the previous adult trials. Treatment related adverse events were all Grade 1 or 2 in severity. More AEs were noted in the TDF treatment group than in the placebo treatment group. Of these AEs, gastrointestinal symptoms including vomiting, gastritis, abdominal pain, diarrhea, and nausea were also identified in the prior adult clinical trials and are included in the product label. Dizziness, increased blood cholesterol and gynecomastia are also included in the product label.

Osteopenia was identified as treatment related in 7% (3 subjects) in the TDF arm and 2% (1 subject) in the placebo arm. The total number of osteopenic events increased when subjects were switched from the placebo arm to open-labeled TDF (2 subjects). Table 25 provides details on treatment emergent treatment related AEs.

Table 25: FDA Analysis Treatment Emergent Treatment Related Adverse Events (RAT population)

Events	**TDF** (N=45) 12 subjects, 14 events	**Placebo** (N=42) 6 subjects, 8 events	**Placebo to TDF Open Label** (N=36) 3 subjects, 3 events
Gastointestinal Disorder	8 (18%)	1 (2%)	0
Vomiting	4 (9%)	0	0
Gastritis	1 (2%)	1 (2%)	0
Abdominal Pain	1 (2%)	0	0
Diarrhea	1 (2%)	0	0
Nausea	1 (2%)	0	0
Bone Disorder	3 (7%)	1 (2%)	2 (6%)
Osteopenia	3 (7%)	1 (2%)	2 (6%)
Neurologic Disorder	0	1 (2%)	0
Pain in Extremity	0	1 (2%)	0
Dizziness	1 (2%)	1 (2%)	0
Renal Disorder	0	2 (4%)	0
Hematuria	0	1 (2%)	0
Nephrolithiasis	0	1 (2%)	0
Blood and Lymphatic Disorder	0	1 (2%)	1 (3%)
Neutropenia	0	1 (2%)	0
Retroperitoneal Lymphadenopathy	0	0	1 (3%)
Reproductive and Breast Disorder	1 (2%)	0	0
Gynecomastia	1 (2%)	0	0
Metabolism and Nutrition Disorders	1 (2%)	1 (2%)	0
Increased Blood Cholesterol	1 (2%)	0	0
Hypertriglyceridemia	0	1 (2%)	0

Source: FDA analysis from AE datasets

7.3.5 Submission Specific Primary Safety Concerns

Previously identified specific TDF safety concerns include: gastrointestinal, renal, bone, and growth AEs. Each was analyzed and data are included in this section.

Gastrointestinal Adverse Events

More subjects in the TDF arm had gastrointestinal AEs than in the placebo arm (Table 26). Abdominal pain, nausea, vomiting, diarrhea and gastritis are consistent with known TDF related AEs. The rates of abdominal pain and vomiting in this adolescent study were higher than those originally reported in the adult clinical trials (24% compared to 15% and 31% compared to 13%, respectively).

Medical Officer Comment: It is difficult to make meaningful cross-study comparisons in different populations. Nonetheless, the rates of abdominal pain and vomiting may be higher in adolescents than in adults.

It is unclear if the higher rate of vomiting in the adolescent trial compared to the adult trial had any effect on efficacy of drug. However, the steady-state PK study provides evidence that if the drug is tolerated, then exposure equals that in adults.

Table 26: Gastrointestinal Adverse Events (RAT analysis population)

Grade 1 and 2 Adverse Events – Preferred Terms	**TDF** (N=45)	**Placebo** (N=42)	**Placebo to Open Label TDF** (N=36)
Vomiting	14 (31%)	4 (10%)	2 (6%)
Abdominal Pain	11 (24%)	5 (12%)	0
Diarrhea	10 (22%)	4 (10%)	5 (13%)
Nausea	10 (22%)	3 (7.1%)	1 (2.8%)
Gastritis	5 (11%)	1 (2.4%)	0
Aphthous stomatitis/Stomatitis	3 (7%)	1 (2%)	1 (3%)
Constipation	3 (7%)	0	0
Dental Caries/Dental Necrosis	2 (4%)	0	0
Chelitis	1 (2%)	1 (2%)	0
Toothache	1 (2%)	2 (4.8%)	0
Gingivitis	0	1 (2%)	0

Source: FDA analysis from Applicant AE datasets

Renal Adverse Events

The rate of renal AEs did not appear to be significantly increased in the TDF arm (Table 27). One subject in the TDF arm developed acute renal failure which was reported as

an SAE. This subject was being treated with amphotericin B for cryptococcal infection at the time of the acute renal failure.

All subjects had normal to low reported values of serum creatinine during the study. There were no clinical or laboratory reported AEs of increased creatinine during the trial. Mean creatinine values increased on study drug but remained within the normal reference range for age (mean creatinine of 0.55 mg/dL to 0.65 mg/dL for subjects on TDF and 0.56 mg/dL to 0.61 mg/dL for subjects on placebo). Median change in estimated creatinine clearance from baseline to week 48 was -11 mL/min/1.73 m^2 for the TDF group and -5.35 mL/min/1.73 m^2 for the placebo group.

Proteinuria was not reported as a clinical AE but was identified in the laboratory AEs. One subject (subject ID [redacted] (b) (6)) in the TDF arm developed proteinuria as an SAE. He was noted to have had evidence of "a high level of" proteinuria (posited by investigators to be due to HIV disease) prior to trial enrollment, but developed worsening proteinuria during an illness with sinusitis and dehydration. Further evaluation with a 24-hour urine collection and additional studies for evaluation of nephritic proteinuria were performed. No further details were available and the event was considered resolved and not related to study medication.

Laboratory AEs revealed 7 subjects with grade 1 proteinuria and 1 subject with grade 2 proteinuria in the TDF arm. In the placebo arm, 2 subjects had reported grade 1 proteinuria. None of these events were considered related to study drug by investigators. One subject in the open labeled TDF treatment group had grade 1 glycosuria. Phosphate and calcium abnormalities are noted in the Bone Adverse Events section. No subjects were reported to have developed any proximal renal tubular defects; however, the urine electrolytes were not measured in the clinical trial.

Table 27: Renal and Urinary Tract Adverse Events (RAT analysis population)

	TDF (N=45)	**Placebo** (N=42)	**Placebo to OL TDF** (N=36)
Renal/Urinary AEs	6 (13.3%)	4 (9.5%)	1 (2.8%)
Grade 1			
Hematuria	2 (4.4%)	2 (4.8%)	1 (2.8%)
Acute Renal Failure	1 (2.2%)	0	0
Pollakiuria	1 (2.2%)	1 (2.4%)	0
Dysuria	1 (2.2%)	0	0
Grade 2			
Proteinuria	1 (2.2%)	0	0
Nephrolithiasis	0	1 (2.4%)	0

Source: Applicant AE datasets

Bone Adverse Events

An FDA internal consultation with experts in bone metabolism and health from the Division of Reproductive and Urologic Products was performed. Dr. Stephen Voss provided this clinical review. For additional details, please refer to Dr. Voss's official consult.

Bone Mineral Density

During the period of adolescence, children are supposed to gain an average of 10-20% BMD. The only reference values available for BMD in the pediatric age range are based on American and European children, primarily Caucasians, and these reference values may not reflect "normal" for Brazilian and Panamanian children. In the HIV-1 infected study subjects, BMD was below average at baseline for both treatment groups. BMD increased less in the TDF treatment group than in the placebo treatment group with some subjects losing BMD. Over the 48 week double-blind treatment period, 6 of 33 TDF subjects (18%) had a significant loss of >4% in lumbar spine BMD (-4.72%, -5.41%, -5.84%, -6.96%, -7.31%, and -7.44%). In contrast, there was only one placebo subject who lost > 4% of spine BMD (-4.27%) during this time period.

Spine and total body Z-scores were low at baseline partly due to delayed skeletal growth, presumably from HIV. There was a trend for Z-scores to decline further during treatment with TDF that cannot be attributed to differences in bone growth (Table 28).

As identified in the adult clinical trials, BMD decreases among adolescents were noted in the first 24 to 48 weeks after starting TDF therapy. Overall, the BMD losses were not statistically significant, however, the study was not powered for this endpoint.

Table 28: L1-L4 Spine BMD – Percent Change from baseline (RAT population)

	TDF + OBR	Placebo + OBR	All TDF
Baseline (BL)			
N	45	42	81
BMD, Mean (SD) (g/cm^2)	0.94 (0.15)	0.95 (0.14)	0.96 (0.15)
p-value: TDF *vs.* placebo*	0.78		
Z-score, Mean (SD)	-1.00 (1.21)	-0.81 (1.41)	
Week 24			
N	44	42	55
Mean % change from BL(SD)	**1.20** (4.96)	**1.93** (4.52)	**1.32** (4.73)
Range	-10.08, 10.54	-6.34, 12.64	-10.08, 10.54
p-value: TDF *vs.* placebo*	0.59		
# with increased BMD	26	27	35
# with decreased BMD	17	14	19
# with > 4% decrease in BMD	6	6	8
Week 48 (LOCF)			
N	44	42	
Mean % change from BL(SD)	**3.16** (6.62)	**3.66** (4.96)	
Range	-7.44, 20.59	-4.27, 14.33	
p-value: TDF *vs.* placebo*	0.64		
# with increased BMD	28	30	
# with decreased BMD	15	12	
# with > 4% decrease in BMD	6	1	
Week 48 (completers)			
N	33	33	61
Mean % change from BL (SD)	**3.15** (7.29)	**3.81** (4.98)	**3.06** (6.23)
Range	-7.44, 20.59	-4.27, 14.33	-7.44, 20.59
p-value: TDF *vs.* placebo*	0.54		
# with increased BMD	20 (61%)	25 (76%)	40
# with decreased BMD	13 (39%)	8 (24%)	19
# with > 4% decrease in BMD	**6 (18%)**	**1 (3%)**	6
Week 96 (open label)			
N			28
Mean % change from BL (SD)			**7.67** (9.74)
Range			-4.12, 32.97
# with increased BMD			21
# with decreased BMD			7
# with > 4% decrease in BMD			1
Week 144 (open label)			
N			4
Mean % change from BL (SD)			**14.93** (16.36)
Range			-4.11, 35.59
# with increased BMD			3
# with decreased BMD			1
# with > 4% decrease in BMD			1

* p-value from Wilcoxon rank sum test
Source: Dr. Voss's consult, CSR and Safety Update, ADDEXA datasets

Biochemical Markers of Bone Turnover

Biochemical changes showed some differences between TDF and placebo in adolescents, with trends similar to adults but generally not statistically significant, again probably due in part to the smaller size of the study. Markers of bone turnover (both formation and resorption) increased in adolescents as they had in adults, however unlike adults, the differences were not statistically significant, and did not appear to be sustained after the first year. As in adults, serum calcium levels increased less with TDF than the control group, with little change overall, despite higher PTH levels. Both hypo- and hypercalcemia were infrequent with TDF, with only one value (6.7 mg/dL) constituting more than a Grade 1 abnormality. As in adults, serum phosphorus levels declined somewhat, especially after 2-3 years on TDF, though only 2 subjects had hypophosphatemia. In other studies, lower serum phosphorus levels appear to be associated with poorer outcomes in terms of bone health and growth.

For the double-blind groups, mean serum calcium concentrations at baseline were 9.38 mg/dL (TDF group) and 9.4 mg/dL (placebo group). At week 48, net increases from baseline were 0.02 mg/dL for the TDF group and 0.18 mg/dL for the placebo group (p=0.23). Corrected for albumin, net changes in serum calcium at week 48 were -0.06 mg/dL for the TDF group and 0.12 mg/dL for the placebo group (p=0.10).

Hypocalcemia (< 8.6 mg/dL) occurred in 8/45 (18%) subjects on TDF and in none on placebo. Seven of these 8 cases were Grade 1 (Ca 7.8-8.5 mg/dL); the other (Subject (b) (6) had one Grade 3 reading (6.7 mg/dL at week 40), and his 8 other readings were between 7.7-9.0 mg/dL including a reading of 8.1 mg/dL drawn 3 days after the lowest reading of 6.7 mg/dL None of these hypocalcemic subjects used calcium, vitamin D, and/or multivitamin supplements in this phase, and all 8 had increases in lumbar spine BMD during the study.

Hypercalcemia (> 10.3 mg/dL) occurred in 3/45 TDF subjects (7%) and 8/42 placebo subjects (19%); all of these were Grade 1 (Ca 10.4-11.5 mg/dL), and only one was > 10.6 mg/dL: a baseline value of 11.1 mg/dL in a TDF subject. None of these subjects used calcium, vitamin D, and/or multivitamin supplements in this phase. Of these 11 hypercalcemic subjects, 6 (1 TDF, 5 placebo) had elevated levels (>65 pg/mL) of serum PTH at least once.

The 120-day safety update also reported 2 additional cases of hypocalcemia and 1 additional case of hypercalcemia in the open label extension; all were Grade 1. Mean changes from baseline serum calcium in this phase at weeks 60, 72, 84, 96, 108, and 120 were -0.002, +0.095, +0.022, +0.006, -0.076, and +0.167 mg/dL respectively.

Mean serum phosphorus concentrations were 4.8 mg/dL (TDF group) and 4.7 mg/dL (placebo group) at baseline, and small mean decreases from baseline were observed at most timepoints for both double-blind groups, with little difference between treatment

groups. At week 48 the mean changes for TDF and placebo were -0.15 and -0.10 mg/dL (NS).

Baseline values for PTH were significantly lower in the TDF group compared to the placebo group (median 38 vs. 47 pg/mL; mean 43 vs. 50 pg/mL, p = 0.033, Wilcoxon rank sum test). During the study there were small increases in PTH in the TDF group compared to small decreases in the placebo group. Median values in all groups and timepoints remained in the normal range.

25OH Vitamin D increased about equally in the two double blind treatment groups to week 48, with increases sustained up to 2-3 years. 1,25-OH vitamin D was not evaluated in this study.

Fractures and Osteopenia Adverse Events

Because of declines in BMD and/or skeletal Z-scores, “osteopenia” was reported as an AE in 3 subjects (6.7%) in the double-blind TDF group; 2 subjects (4.8%) in the double-blind placebo group; and 5 subjects (6.2%) in the All-TDF group.

Medical Officer Comment: The definition for osteopenia was not a standardized definition in the trial protocol. Determination and report of osteopenia as an adverse event was based on investigator discretion.

Two fracture AEs (reported as non-serious and non-study drug-related) were reported for subjects in the TDF group (compared with none with placebo); both fractures were trauma related. Subject (b) (6), a 14-year old male, had a clavicle fracture on day 164; his Z-scores on day 172 were -0.403 spine, -1.313 total body, both improved from baseline. Subject (b) (6), a 15-year old female, had an ankle fracture on day 175. The narrative states that she “rotated” her foot while playing on an elastic bed, and the orthopedist considered this history to be characteristic for the type of fracture. This subject had an ongoing AE of “osteopenia” at the time of the fracture, having entered the study with low Z-scores (-1.633 spine, -2.176 total body) which had further declined (to -2.140 spine, -2.665 total body) just prior to the fracture. Neither of these fracture patients had been on steroids or other medications likely to affect bone, or had prior history of fracture. There were no additional fractures or AEs of “osteopenia” reported in the 120-day safety report.

Growth Adverse Events

Height and weight were monitored during the clinical trial. Subjects were below average in both height and weight at baseline. Overall, no clinically relevant differences were noted between treatment groups in height or weight. Baseline body height Z-score means were -1.09 for the TDF group and -0.92 for the placebo group. Baseline body weight Z-score means were -1.03 for the TDF group and -0.5 for the placebo group.

Mean body height Z-score at week 48 had increased slightly in the TDF group (+0.07 SD) with a slight drop in the placebo group (-0.01 SD). Mean body weight Z-score changes at week 48 were -0.06 SD and -0.02 SD for the TDF and placebo groups, respectively.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events of grade 2 or greater severity regardless of relationship to study drug occurring in ≥5% of subjects included: sinusitis, pneumonia, gastritis, vomiting, neutropenia, and dizziness (Table 29). Sinusitis and pneumonia were attributed to underlying immune status. Neutropenia was attributed to zidovudine as part of the OBR. Gastrointestinal disorders and nervous system disorders were recognized in the adult trials and included in the label. Jaundice was reported in both treatment arms. On further evaluation of hyperbilirubinemia, almost all subjects were on atazanavir as part of their OBR and hyperbilirubinemia and jaundice are labeled AEs of atazanavir.

Table 29: Treatment Emergent Adverse Events (Grades 2-4) Reported in >5% in Any Treatment Group (RAT population)

Adverse Event (Grade 2-4)– Preferred Term	**TDF** (N=45)	**Placebo** (N=42)
Infections/Infestations	71%	43%
Sinusitis	9%	7%
Pneumonia	7%	5%
Gastrointestinal Disorders	29%	10%
Gastritis	7%	0
Vomiting	7%	5%
Blood Disorders	7%	0
Neutropenia	7%	0
Nervous System Disorders	9%	12%
Dizziness	7%	5%
Hepatobiliary Disorder	4%	7%
Jaundice	4%	7%

Source: CSR, AE dataset

7.4.2 Laboratory Findings

The laboratory abnormalities identified in this clinical trial are consistent with those previously identified in the adult clinical trials. The laboratory abnormalities associated with bone mineralization are discussed in detail in section 7.3.5.

Evaluation for drug induced hepatotoxicity did not reveal a safety concern. Evaluation was performed by identifying subjects with transaminase and bilirubin elevations without elevated alkaline phosphatase. Two subjects in the TDF treatment arm had elevated transaminases and total bilirubin (grade 2 toxicities) without elevation of alkaline phosphatase. One of these subjects was co-infected with hepatitis C and had grade 2 AST and ALT elevation (AST 123 units/L, ALT 112 units/L) with total bilirubin level of 2.9 mg/dL. The other subject had AST of 80 units/L, total bilirubin of 1.85 mg/dL and was taking ritonavir-boosted atazanavir, abacavir, and lamivudine as her OBR. Hyperbilirubinemia is a known AE of atazanavir and elevations in transaminases are not uncommon with ARVs.

The grade 3 and 4 laboratory AEs were evaluated and are represented in Table 30. Overall, more subjects in the TDF treatment group experienced neutropenia. Some of the neutropenia could be explained by presence of zidovudine in subjects' OBR. TDF treated subjects also had more hyperbilirubinemia events than placebo treated subjects. In almost all of these cases, subjects were also taking atazanavir as part of their OBR.

Neutropenia, hypercholesterolemia, and hypertriglyceridemia were identified in TDF treated subjects in the adult trials and appear in the label.

Table 30: Treatment Emergent Grade 3-4 Laboratory Abnormalities (RAT population)

Laboratory Assessment with Grade 3 or 4 Abnormality	TDF (N=45)	Placebo (N=42)	All TDF (N=81)
Neutropenia			
Grade 3	4 (8.9%)	1 (2.4%)	6 (7.4%)
Grade 4	3 (3.6%)	1 (2.4%)	3 (3.7%)
Elevated ALT			
Grade 3	0	1 (2.4%)	0
Hypocalcemia			
Grade 3	1 (2.2%)	0	1 (1.2%)
Creatine Kinase Elevation			
Grade 4	0	1 (2.4%)	0
Hyperbilirubinemia			
Grade 3	3 (6.7%)	1 (2.4%)	3 (3.7%)
Grade 4	1 (2.2%)	3 (7.1%)	2 (2.5%)
Hypercholesterolemia (Fasting)			
Grade 3	0	1 (2.4%)	0

Source: CSR, Lab dataset

7.4.3 Vital Signs

Changes in growth are discussed in section 7.3.5. There were no clinically relevant differences between treatment groups in changes from baseline in vital signs.

8 Postmarket Experience

A Pediatric Safety Review of TDF was performed from the Gilead Drug Safety and Public Health (DSPH) database through March 31, 2009. Sixty-nine SAEs were reported from children less than 18 years of age on TDF. Of these, renal disorders were the most frequently reported events (31 of 69 cases, 45%). Twenty-one had evidence of possible causal association with TDF. Many of these cases involved pediatric patients receiving a higher dose than that selected for the pediatric clinical trials (8mg/kg up to 300mg/day). Renal events were consistent with those reported in adults: proximal renal tubulopathy (n = 7), hypophosphatemia/decreased serum phosphate (n = 5), Fanconi syndrome (n = 4), nephrogenic diabetes insipidus (n = 3), increased serum creatinine (n = 2), renal failure (n = 2), renal insufficiency (n = 1). Four reports of bone events associated with proximal renal tubulopathy were also received (rickets [n = 3] and osteomalacia [n = 1]), which are consistent with that observed in adults.
Six cases of decreased BMD were received, which were all reported as SAEs from studies. In three of these six patients, the decreases in BMD were small (1 – 5%). In the three remaining cases, BMD decreased by 9%, 10% and 27%. The child who experienced the 27% decrease in BMD was 11 years old and appeared to have received an overdose of TDF (300mg; 345 mg/m^2).

Other events reported in 39 of the 69 pediatric cases included hepatic events (n = 4), gastrointestinal events (n = 6), skin events (n = 8), blood events (n = 12), eye events (n = 3), cardiovascular events (n = 4) or isolated reports of other events (n = 5). In 32 of these 39 cases (82%), the evidence provided did not support a causal association with TDF or the cases were poorly documented. In the remaining cases (7/39, 18%), the events were consistent with the safety profile of TDF.

The profile of adverse events with a possible association to TDF in pediatric cases from the DSPH safety database was consistent with the current TDF core safety information. No safety issues specific to children were identified.

9 Appendices

9.1 Literature Review/References

Literature review from the Applicant was relatively inclusive. Additional scientific publications were identified during this clinical reviewer's literature search. These

publications describe TDF adverse events specifically in regards to renal proximal tubular disorders including Fanconi syndrome and losses in BMD, osteoporotic fractures and osteomalacia. Most of these reports have been in adults. These reports in the literature taken together with the post-marketing reports identified by the Applicant provide additional information regarding bone and renal toxicity associated with TDF. One in vitro study evaluating the direct cytotoxic effects on osteoclasts provides insight into one of the possible mechanisms of TDF bone toxicity. Additional studies are warranted. See section 1.4 for post marketing commitments and requirements.

9.2 Labeling Recommendations

Recommended changes to the label include:

- Addition of adolescent specific BMD findings in the Warnings and Precautions section

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

  In a clinical study of HIV-1 infected adolescent subjects in Study 321, bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in adolescents. In this study, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD treated adolescents and one placebo treated adolescent had significant (>4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults.

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

- Move the adolescent clinical trial description from the clinical section to the section Use in Special Populations: Pediatrics.

- (b) (4)

"Adolescent Patients

The safety of VIREAD in adolescent patients aged 12 to <18 years is supported by data from one randomized study in which VIREAD was administered to HIV-1 infected treatment-experienced subjects. In this study, the pharmacokinetic profile of VIREAD was similar to that found to be safe and effective in adult clinical trials.

In Study 321, 87 treatment-experienced subjects 12 to <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 adolescent subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of VIREAD in patients ≥12 years of age who weigh ≥35 kg and whose HIV-1 isolate is expected to be sensitive to VIREAD. *[See WARNING AND PRECAUTIONS (5.6), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)].*

Safety and effectiveness in patients less than (b) (4) *12 years of age have not been established."*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21356	SUPPL-33	GILEAD SCIENCES INC	VIREAD(TENOFOVIR DISOPROXIL FUMARATE)300

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/s/

REBECCA E LEVORSON
03/23/2010