OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA(s)	**22577 (oral powder) & 21356 S038 (reduced tablet strengths)**
Submission Date	**June 16, 2011 (accepted July 18, 2011)**
Brand Name	**Viread®**
Generic Name	**Tenofovir disoproxil fumarate**
Reviewer	**Dionna Green, M.D.**
Team Leader	**Sarah Robertson, Pharm.D.**
OCP Division	**DCP IV**
OND Division	**DAVP**
Sponsor	**Gilead**
Relevant IND(s)	**52,849**
Submission Type; Code	**Pediatric supplement**
Review Type(s)	**Priority**
Formulation(s); Strength(s) to-be-marketed	**Oral powder (40 mg/1 gm); tablets (150, 200, and 250 mg)**
Currently Marketed Formulation(s)	**Tablet (300 mg)**
Approved Dosing Regimen	**300 mg once daily (for adults and pediatric patients 12 to <18 years old)**
Proposed Dosing Regimen	**8 mg/kg (up to a maximum of 300 mg) once daily**
Proposed Indication	**Treatment of HIV-1 infection in pediatric patients 2 to < 12 years old**

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1 EXECUTIVE SUMMARY

Tenofovir disoproxil fumarate (TDF, Viread®) is the prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor, and is currently indicated for the treatment of chronic hepatitis B (HBV) in adults and for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (12 to <18 years of age). The recommended dosing regimen for TDF in the treatment of HIV-1 in both adults and adolescents is 300 mg once daily. Currently, a 300 mg strength tablet is the only commercially available formulation of TDF. In this current submission, the Applicant is seeking to extend dosing to HIV-infected pediatric patients 2 < 12 years of age using new formulations of TDF: TDF oral powder (40 mg/1 gm) and reduced-strength TDF tablets (150, 200, and 250 mg) and a dosing regimen of: TDF 8 mg/kg (up to a maximum of 300 mg) once daily.

Two pivotal trials provide support for this application. The first (GS-US-104-0312) was a bioequivalence study bridging the tenofovir DF oral powder formulation to the marketed 300 mg tablet in healthy adult subjects. A second trial (GS-US-104-0352) evaluated the PK, safety, and efficacy of the TDF oral powder formulation in HIV-infected pediatric subjects ages 2 to <12 years.

A biowaiver was requested in lieu of conducting an *in vivo* bioequivalence study for the introduction of the reduced-strength tablets on the basis of *in vitro* comparative dissolution studies and compositionally proportional formulation to the 300 mg tablet strength. The biowaiver was reviewed by Arzu Selen, Biopharmaceutics reviewer in the Office of New Drug Quality Assessment (ONDQA) and was deemed acceptable (see review by Dr. Selen).

The proposed dosing recommendations for the oral powder and reduced-strength tablets are displayed below in **Table 1** and **Table 2**, respectively.

Table 1 – TDF Dosing Recommendations for Pediatric Subjects ≥ 2 Years of Age (Oral Powder)

Body Weight	**Oral Powder Once Daily**
Kilogram (kg)	Scoops of Powder[a]
10 to <12	2.0
12 to <14	2.5
14 to <17	3.0
17 to <19	3.5[b]
19 to <22	4.0[b]
22 to <24	4.5[b]
24 to <27	5.0[b]
27 to <29	5.5[b]
29 to <32	6.0[b]
32 to <34	6.5[b]
34 to <35	7.0[b]
≥35	7.5[b]

a Each scoop delivers 1 gram of powder which contains 40 mg of TDF
b Option to use tenofovir DF oral powder for subjects unable to swallow tablets.

Table 2 – TDF Dosing Recommendations for Pediatric Subjects ≥ 2 Years of Age and Weighing ≥ 17 kg (Tablets)

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

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted in NDA 22577 and NDA 21356 S-038 and agrees that it supports the proposal to introduce dosing of TDF 8 mg/kg (up to a maximum of 300 mg) once daily for children 2 to <12 years of age using the new TDF oral powder and reduced-strength tablet formulations.

The NDA and sNDA are approvable from a clinical pharmacology perspective. Edits to the proposed label are recommended (See Section 3).

1.2 Phase IV Commitments

None

1.3 Summary of Key Clinical Pharmacology and Biopharmaceutics Findings

TDF is approved for the treatment of chronic HBV in adults and for the treatment of HIV-1 in both adults and adolescents (12 to < 18 years of age) at a recommended dose of 300 mg once daily. This current submission includes the introduction of new TDF formulations in order to provide age-appropriate formulations for HIV-infected pediatric patients 2 years of age and older and who weigh at least 10 kg.

This application is supported by two pivotal trials. Study GS-US-104-0352 evaluates the oral powder formulation and provides pivotal PK, safety, and efficacy data in children. Study GS-US-104-0312 is a BE study that bridges the TDF oral powder formulation to the highest strength TDF tablet (300 mg) formulation in healthy adult subjects and therefore, provides a pivotal link to support the introduction of the reduced-strength tablets (150, 200, and 250 mg) and allows them to be used interchangeably with the oral powder in children able to swallow intact tablets. The reduced strength tablets have not been evaluated in pediatric subjects. The sponsor is requesting a biowaiver of *in vivo* bioequivalence studies for the TDF reduced-strength tablets on the basis of *in vitro* comparative dissolution studies and compositionally proportional formulation to the 300 mg tablet strength. This review summarizes the clinical pharmacology results from Studies 0352 and 0312.

Reviewer comment: Initial PK and safety studies (GS-01-926 and GS-01-927) of TDF in HIV-1 infected pediatric subjects (total N=25; age range 6 to 16 years old) were conducted using investigational 75 mg strength tablets. These two studies explored doses ranging from 3 to 10 mg/kg and demonstrated that exposures achieved following a dose of TDF 8 mg/kg best matched effective adult exposures achieved following a 300 mg dose. As a result, an 8 mg/kg dose was selected to be carried into the Phase 3 study.

Study GS-US-104-0352

A Phase 3 PK, safety, and efficacy study was conducted in children 2 to < 12 years of age in which the TDF oral powder formulation was evaluated (Study GS-US-104-0352). In study 0352, treatment-experienced subjects (N=97) who were naïve to TDF therapy were randomized (1:1 ratio) to either continue their current therapy of a stavudine- or zidovudine-containing antiretroviral regimen or switch to a TDF-containing antiretroviral regimen at a TDF dose of 8 mg/kg (up to a maximum of 300 mg) once daily utilizing the TDF oral powder formulation. Patients weighing > 37 kg and who could swallow an intact tablet received the 300 mg tablet formulation.

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at week 48. Secondary endpoints included the proportion of subjects with HIV-1 RNA < 50 copies/mL and change from baseline in CD4 cell count and CD4 percentage. At Week 48, 83.3% of subjects in the TDF group and 91.8% of subjects in the stavudine or zidovudine group had HIV-1 RNA < 400 copies/mL. The difference in percentage of subjects

with HIV-1 RNA < 400 copies/mL between TDF and stavudine or zidovudine groups was -8.5% and the 95% CI was -21.5% to 4.5%. TDF did not meet the criteria for treatment noninferiority (NI) at Week 48 since the lower bound of the CI for the differences between treatment groups was less than the pre-specified NI margin of -0.15. However, when using a post-hoc analysis (the snapshot algorithm) that evaluated the virologic endpoint over a specified window of time it was noted that the difference in response between the two treatment groups did meet the NI margin (see Clinical and Biometrics reviews by Dr. Vargas-Kasambira and Dr. Zeng, respectively). The safety findings in study 0352 including the findings in the 96-week extension phase were consistent with findings seen in both adults and adolescents.

Tenofovir PK was evaluated in a subset of 23 children in study 0352 who had received TDF oral powder 8 mg/kg once daily for at least 4 weeks.
Figure 1 displays the mean plasma concentrations of tenofovir by age group (2 to <6 years and 6 to <12 years).

Table 3 summarizes the mean steady-state PK parameters of tenofovir in the PK subset overall and by age group. **Table 4** summarizes historical steady-state tenofovir PK parameters observed at varying time points in HIV-1 infected adults (Studies GS-97-901 and GS-99-907).

Figure 1 – Mean Plasma Concentrations of Tenofovir in HIV-1 Infected Children by Age Group

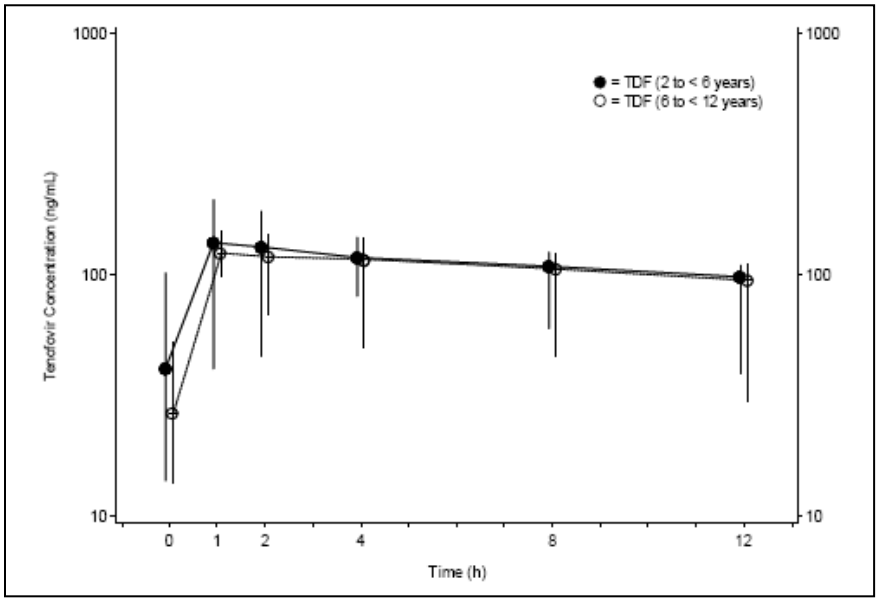


Table 3 – Summary of Steady-State PK Parameters for Tenofovir in HIV-1 Infected Children

TFV Plasma PK Parameter (Units)	Tenofovir DF 8 mg/kg		
	Overall (N = 23)	2 to < 6 years (N = 12)	6 to < 12 years (N = 11)
AUC_{tau} (ng•h/mL)[a] Mean (% CV)	2586.3 (40.9)	2679.1 (39.9)	2485.0 (43.8)
AUC_{last} (ng•h/mL) Mean (% CV)	1704.4 (42.9)	1780.6 (43.5)	1621.3 (43.8)
C_{max} (ng/mL) Mean (%CV)	238.7 (53.4)	257.2 (58.9)	218.5 (44.8)
C_{tau} (ng/mL)[a, b] Mean (%CV)	54.5 (43.4)	55.4 (47.3)	53.4 (41.0)
CL/F (L/h)[a] Mean (%CV)	34.7 (71.4)	22.7 (40.6)	47.8 (62.5)
T_{max} (h) Median (Q1, Q3)	1.93 (1.08, 2.30)	1.98 (1.20, 2.24)	1.22 (1.00, 4.00)
T_{last} (h) Median (Q1, Q3)	12.00 (12.00, 12.00)	12.00 (12.00, 12.05)	12.00 (12.00, 12.00)
$T_{½}$ (h)[a, c] Median (Q1, Q3)	13.65 (11.43, 16.00)	13.85 (9.96, 16.54)	12.31 (11.43, 15.99)

a Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour timepoint.

b 2 to < 6 years: N = 11. For Subject 1678-9085, predose concentration was not used as the surrogate 24-hour timepoint since the last observed concentration at the 12.02-hour timepoint was lower than the predose concentration. 6 to < 12 years: N = 10. For Subject 1578-9050, predose concentration was below limit of quantitation. 2 to < 12 years (total): N = 21

c 2 to < 6 years: N = 11. For Subject 1578-9016, lambda z (h-1) and T½ (h) were not calculable. 2 to < 12 years (total): N = 22

Table 4 – Summary of Steady-State PK Parameters for Tenofovir in HIV-1 Infected Adults

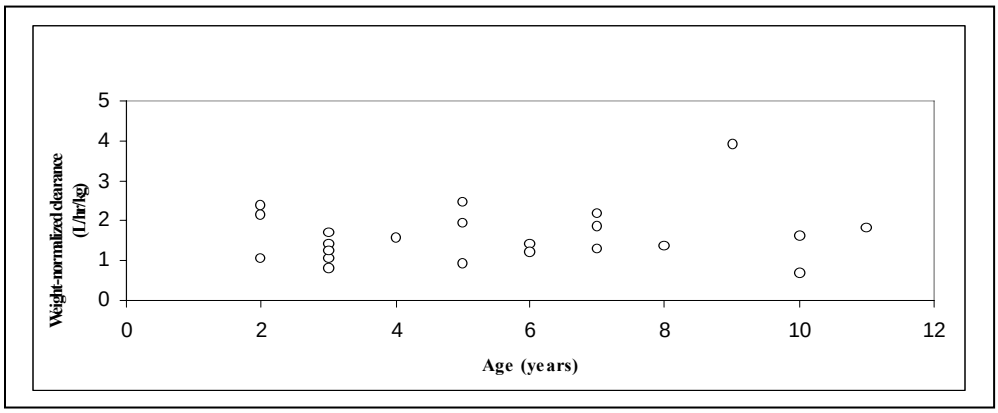
TFV Plasma PK Parameter (Units)	GS-97-901 300 mg/day		GS-99-907 300 mg/day			
	8th Dose (N = 8)	28th Dose (N = 8)	12 Weeks (N = 12)	24 Weeks (N = 12)	36 Weeks (N = 7)	48 Weeks (N = 7)
AUC_{tau} (ng•h/mL) Mean (% CV)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL) Mean (%CV)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h) Median (Q1, Q3)	13.7	14.4	14.0	14.9	12.4	14.5

Reviewer Comment: In the PK substudy of study 0352, a dose of 8 mg/kg TDF oral powder once daily for 4 weeks yielded mean steady-state exposures (AUC_{tau}) in children 2 to <6 years and 6 to <12 years of age that were lower by 11% and 18%, respectively, when compared to historical mean steady-state exposures observed in adults who were administered TDF 300 mg once daily for 4 weeks. When investigating the differences in exposures between the two age cohorts, an outlier (Subject 9050 – a 9 y/o male with an individual AUC_{tau} value over 2.5 times lower than the mean AUC for the cohort) was identified in the pediatric PK dataset. Removal of this subject from the dataset reduced the difference in mean AUC_{tau} between children 6 to <12 years and adults from 18% to approximately 12%. Furthermore, when comparing overall exposures in children 2 to <12 years to the lower end of the range of steady-state exposures observed in adult historical data (AUC_{tau}: 2742-3297 ng·h/mL), the difference in mean exposures between children and adults was reduced to 3%. It should also be noted that protocols for historical PK studies conducted in adults specified that TDF was to be administered following a high-fat meal, while the pediatric PK study protocol did not specify a meal type. There is a known food-effect for TDF tablets. Administration of TDF tablets following a high-fat meal increases tenofovir AUC and C_{max} by approximately 40% and 14%, respectively, relative to fasting or a light meal. The difference in administration of TDF in the PK study in adults and children may have contributed toward the difference in tenofovir exposures.

Nonetheless, the difference in mean AUC_{tau} values between adults and pediatric is small and would not be expected to result in a clinically significant shift in efficacy. When subjects in the pediatric PK substudy were broken down into 3 groups based on exposures (high, mid, low) there was no clear correlation between AUC value and clinical outcome. In addition, of the 19 virologic failures in study 0352, no cases of tenofovir resistance were identified. This suggests that children in this study were not exposed to suboptimal doses of TDF for prolonged periods of time. (It should be noted that one subject, Subject 9093, in the TDF treatment group had an increase in viral load early in the study and was discontinued from the study at Week 4. Genotyping of a plasma sample from this subject revealed HIV RT mutations K65R and Y181C. This rapid detection of HIV resistance mutations by Week 4 was more likely indicative of preexisting resistance at study entry than suboptimal exposures). Thus, the totality of the pharmacokinetic data supports dosing in children 2 to < 12 years of age at a dose of TDF 8 mg/kg (up to maximum of 300 mg) once daily.

Figure 2 represents the weight-normalized tenofovir clearance by age observed in the pediatric PK substudy.

Figure 2 – Weight-normalized Tenofovir Clearance vs. Age



Reviewer Note: In subjects 2 to <12 years of age, tenofovir clearance was similar when normalized for weight. This provides further support for the conclusion to recommend the same mg/kg TDF dose across this age range.

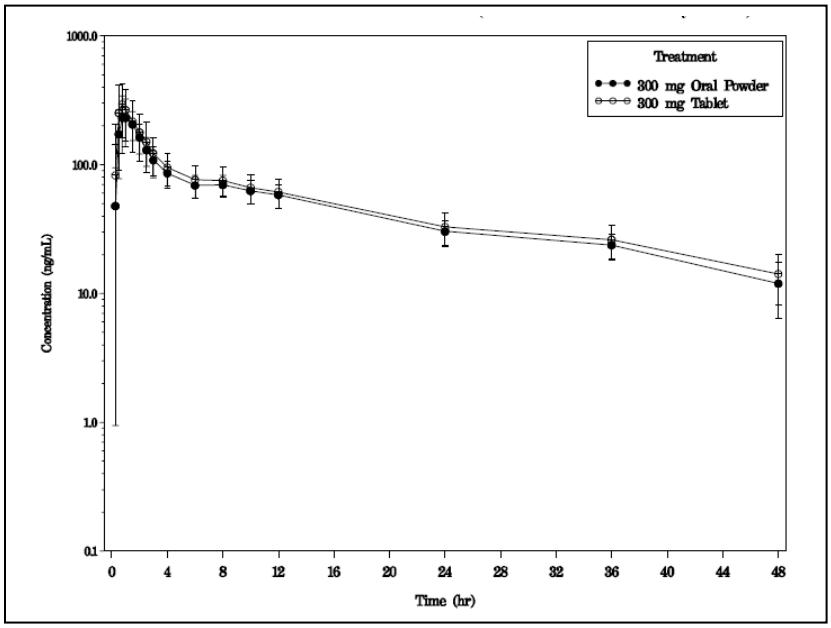
For Study 0352, the Office of Scientific Investigations (OSI) was requested to conduct inspections of the clinical site where the PK substudy was conducted (Clinical Site# 1578, Panama City, Panama) and of the bioanalytical laboratory that analyzed the tenofovir plasma samples (Gilead Sciences, Inc., Durham, NC). Following these inspections, the OSI Reviewer concluded that the PK data from the clinical and bioanalytical portions of the study are acceptable for Agency review. The results of these inspections are discussed in further detail in the individual trial review (see Section 4).

Study GS-US-104-0312

Study GS-US-104-0312 was a bioequivalence study comparing the tenofovir exposures obtained following administration of a 300 mg dose of TDF oral powder and the 300 mg strength TDF tablet in 32 healthy adult male and female subjects (30 of whom completed the study). This study included a 2-way crossover design in which subjects were randomized (1:1 ratio) to either Group A (received oral powder on Day 1 and tablet on Day 8) or Group B (received tablet on Day 1 and oral powder on Day 8). Subjects fasted on Day 0 and Day 8 and a 7-day washout period was provided between treatments. The 300 mg oral powder dose was administered orally mixed in 4 ounces of applesauce followed by 240 mL of water, while the 300 mg tablet was administered orally with 240 mL of water and within 5 minutes of consuming 4 ounces of applesauce. Pharmacokinetic blood sampling took place over a 48-hour period after dosing on Day 1 and Day 8.

The mean and standard deviation of plasma tenofovir concentration-time profiles are shown in **Figure 3**.

Figure 3 – Mean and Standard Deviation of Plasma Tenofovir Concentration-Time Profiles for Oral Powder and Tablet Formulations



Error! Not a valid bookmark self-reference. provides a summary of tenofovir pharmacokinetic parameters following administration of the TDF oral powder and tablet formulations.

Table 5 – Summary of Tenofovir PK Parameters

Tenofovir Pharmacokinetic Parameter	Tenofovir DF Oral Powder 300 mg (N = 30)	Tenofovir DF Tablet 300 mg (N = 30)
C_{max} (ng/mL), Mean (% CV)	272.2 (36)	368.8 (29)
T_{max} (h), Median (Min, Max)	1.00 (0.25, 2.00)	0.75 (0.50, 2.50)
$AUC_{0\text{-last}}$ (h•ng/mL), Mean (% CV)	2144.0 (22)	2376.1 (25)
AUC_{inf} (h•ng/mL), Mean (% CV)	2518.1 (20)	2820.8 (25)
$T_{½}$ (h), Median (Min, Max)	17.8 (14.0, 25.9)	17.8 (10.3, 28.1)
V_z/F (L), Mean (% CV)	1451.9 (25)	1379.8 (31)
CL/F (mL/min), Mean (% CV)	928.1 (20)	889.9 (51)

Table 6 displays the geometric least-squares mean ratios for tenofovir from tenofovir DF oral powder formulation compared to tenofovir DF tablet formulation which were 73% for C_{max}, 93% for $AUC_{0\text{-last}}$, and 92% for AUC_{inf}. The 90% CIs for the geometric mean ratios were

contained within the equivalence bounds of 80% to 125% for $AUC_{0\text{-last}}$ and AUC_{inf}, but not for C_{max} (lower bound 66%).

Table 6 – Statistical Comparisons of Tenofovir PK Parameters for Oral Powder vs. Tablet

Tenofovir Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		Geometric Least Squares Mean Ratio (%)	90% CI
	Tenofovir DF Oral Powder 300 mg (N = 30)	Tenofovir DF Tablet 300 mg (N = 30)		
C_{max} (ng/mL)	258.27	353.39	73.08	66.04, 80.88
$AUC_{0\text{-last}}$ (h•ng/mL)	2106.22	2262.15	93.11	83.39, 103.96
AUC_{inf} (h•ng/mL)	2486.18	2706.66	91.85	83.37, 101.21

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on the natural logarithmic scale.

<u>Reviewer comment</u>: *Tenofovir C_{max} was 27% lower following administration of the TDF oral powder formulation relative to that of the tablet formulation. This difference is likely a result of slower absorption of the oral powder formulation due to the surrounding granule encapsulating technology used for taste masking. The 90% CI for the geometric mean ratio for AUC were contained within 80% to 125%. . TDF is a prodrug which is converted to its active moiety tenofovir diphosphate intracellularly. The active moiety has a longer half life intracellularly compared to tenofovir in plasma. For the NRTI class of drugs, AUC is generally considered the more relevant parameter of exposure, as it pertains to efficacy, and thus the failure of the oral powder and tablet formulation to meet the bioequivalence criteria of the 90% CIs for C_{max} contained within 80% and 125% is not expected to be clinically relevant.*

For Study 0312, the Office of Scientific Investigations was requested to conduct inspections of the clinical site where the BE study was performed (Comprehensive Clinical Development, Tacoma, WA) and the bioanalytical laboratory that analyzed the tenofovir plasma samples (Gilead Sciences, Inc., Durham, NC). Following these inspections it was concluded by the OSI Reviewer that the data from the clinical portion of Study 0312 is acceptable for Agency review. However, in terms of the analytical portion of the study, it was determined that the accuracy of pharmacokinetic measurements for two subjects in the study (subjects 20 and 21 – whose samples were re-injected multiple times) could not be assured due to failure of the site to conduct a re-injection reproducibility experiment during pre-study method validation for the tenofovir LC-MS/MS method. Therefore, it was concluded by the OSI Reviewer that the data for subjects 20 and 21 should be excluded from the bioequivalence assessment.

Reviewer comment: A re-analysis of the data obtained from Study 0312 was performed by this Reviewer following the removal of subjects 20 and 21 from the dataset. The mean and standard deviation of plasma tenofovir concentration-time profiles for the oral powder and tablet formulations are shown in **Figure 4**.

Table 7 *provides a summary of tenofovir pharmacokinetic parameters following administration of the TDF oral powder and tablet formulations.*

Figure 4 – Mean and Standard Deviation of Plasma Tenofovir Concentration-Time Profiles for Oral Powder and Tablet Formulations (Re-analysis following removal of subjects 20 and 21 from dataset)

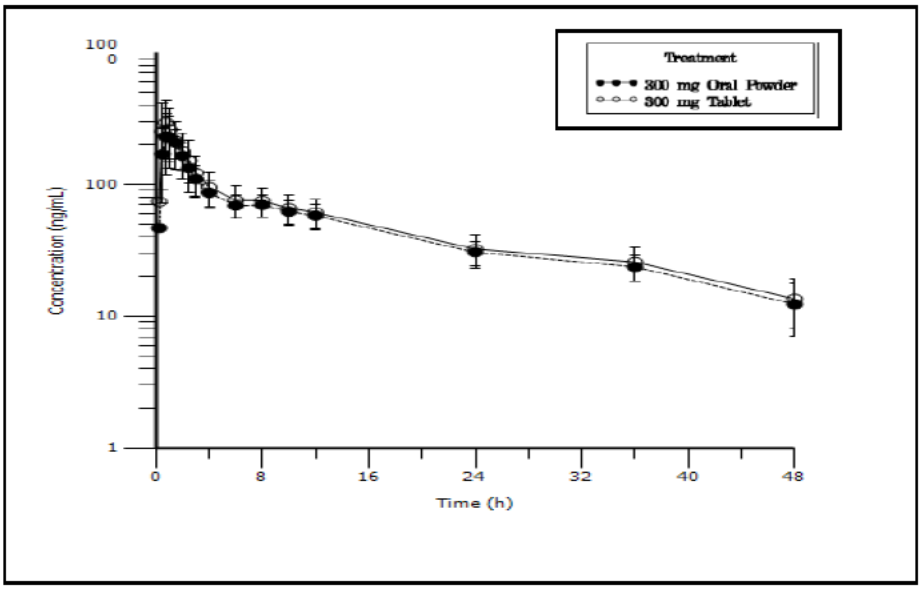


Table 7 – Summary of Tenofovir PK Parameters (Re-analysis following removal of subjects 20 and 21 from dataset)

Tenofovir Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		Geometric Least Squares Mean Ratio (%)	90% CI
	Tenofovir DF Oral Powder 300 mg (N=28)	Tenofovir DF Tablet 300 mg (N=28)		
C_{max} (ng/mL)	257.29	347.52	74.04	66.50, 82.43
$AUC_{0\text{-last}}$ (h•ng/mL)	2146.61	2270.13	94.56	84.15, 106.26
AUC_{inf} (h•ng/mL)	2512.01	2657.10	94.54	84.72, 105.49

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on the natural logarithmic scale.

Reviewer comment (cont.): The removal of subjects 20 and 21 from the dataset did not result in a significant change to the results of the study and did not change the conclusion of the study.

2 QUESTION-BASED REVIEW

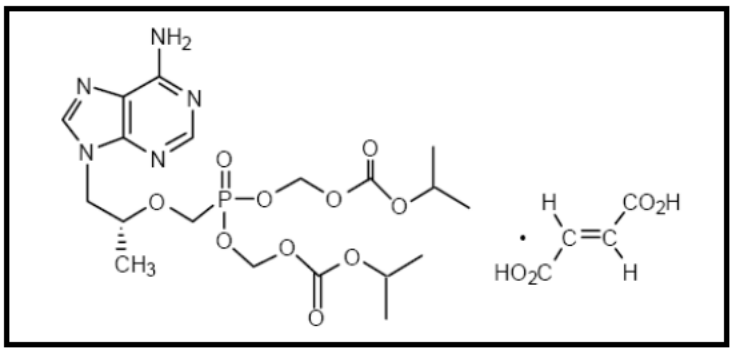
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Tenofovir disoproxil fumarate is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. TDF is currently commercially available as a tablet formulation.

Chemical name: 9-[2-(R)-[[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinoyl] methoxy]propyl]adenine fumarate

Structure:



Molecular formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$
Molecular weight: 635.52
Formulation: tablets, oral powder
Composition: TDF 150, 200, 250, and 300 mg tablets

	Unit Formula					
Component	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**		**%w/w**
Core Tablet						
Tenofovir Disoproxil Fumarate[a]	150.0	200.0	250.0	300.0		(b) (4)
Pregelatinized Starch	(b) (4)					
Croscarmellose Sodium[b]						
Lactose Monohydrate[a]						
Microcrystalline Cellulose[b]						
Magnesium Stearate						
(b) (4)						
Core Tablet Weight						
Film Coating Components						
Opadry II Blue Y-30-10671-A[d]	NA	NA	NA	(b) (4)		
Opadry II White 32K18425[e]	(b) (4)					
(b) (4)						
Total Tablet Weight						-

NA = not applicable

(b) (4)

Composition: TDF oral powder (40mg/1gm)

Component	Amount per Bottle (g/bottle)
Tenofovir DF[a]	(b) (4)
Mannitol	
Hydoxypropyl Cellulose	
Ethylcellulose	
Silicon Dioxide	

(b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

TDF is an oral prodrug of tenofovir. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, the active moiety. Tenofovir is a nucleotide analogue reverse transcriptase inhibitor which inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

Approved therapeutic indications for TDF include the treatment of HIV-1 and chronic Hepatitis B viruses.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage of TDF oral powder for children 2 to <12 years of age and weighing < 35 kg is 8 mg/kg TDF up to a maximum dose of 300 mg once daily taken with soft food. For pediatric patients weighing >17 kg and who can swallow an intact tablet, the proposed dosage is one TDF tablet (~8 mg/kg, rounded to the nearest 150, 200, 250, or 300 mg) once daily taken without regard to food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

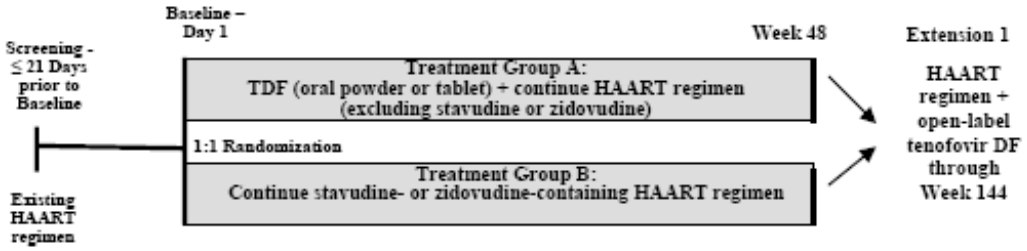
The following studies were used to support dosing or dosing claims:

Pivotal clinical trials

Study GS-US-104-0352 is a 48-week, randomized, open-label, Phase 3 study in treatment-experienced children 2 to < 12 years of age with stable virologic suppression on a stavudine- or zidovudine-containing HAART regimen. The primary objective of this study was to assess the

efficacy of switching to a TDF-containing HAART regimen compared to continuing a stavudine- or zidovudine-containing HAART regimen in maintaining virologic suppression (defined as < 400 copies/mL of HIV-1 RNA at Week 48). The randomized phase was followed by a 96-week, open-label extension phase to evaluate the long-term safety, efficacy, and tolerability of TDF. A total of 100 evaluable subjects were planned for this study. The design schema for Study 352 is shown in **Figure 5** below:

Figure 5 – Study GS-US-104-0352 Schema

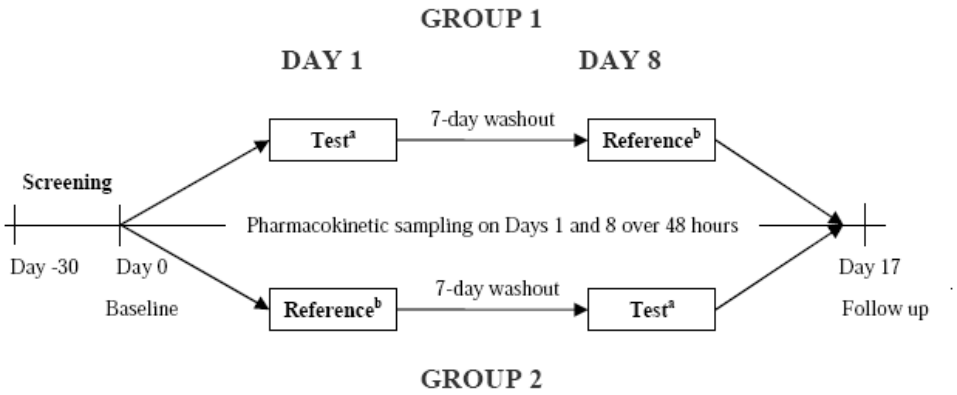


The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48. Secondary endpoints included the proportion of subjects with HIV-1 RNA < 50 copies/mL and change from baseline in CD4 cell count and CD4 percentage.

As a secondary objective of this study, the pharmacokinetics of tenofovir was evaluated in a subset of 23 HIV-1 infected children who had received the TDF oral powder formulation daily at a dose of 8 mg/kg for at least 4 weeks. Pharmacokinetic sampling occurred over a period of 12 hours. Blood samples were collected at the following time points: 0, 1, 2, 4, 8, and 12 hours after TDF dosing.

Study GS-US-104-0312 is a Phase 1 study in healthy adult volunteers intended to evaluate the relative bioavailability and bioequivalence between the investigational TDF oral powder formulation and the commercially available TDF 300 mg tablet formulation. This was a 17-day, open-label, two-way crossover, study in which subjects were randomized to either Group 1 (receive the test product on Day 1 and the reference product on Day 8) or Group 2 (receive the reference product on Day 1 and the test product Day 8). Pharmacokinetic blood sampling took place over a 48 hour period after dosing on Days 1 and 8. A 7-day washout period was provided in between treatments. The design schema for Study 0312 is shown in **Figure 6** below:

Figure 6 – Study GS-US-104-0312 Schema



2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints for TDF used for the basis of the original NDA approval were virologic response (defined as HIV-1 RNA <400 copies/mL) and increase in CD4 counts after 48 weeks of treatment. HIV-1 RNA viral load is a validated surrogate endpoint for clinical outcomes associated with the virus. High viral load correlates with mortality and morbidity, while CD4 counts are an indication of immune status. In study 0352 in pediatric subjects 2 to <12 years of age, the primary endpoint was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

Yes, tenofovir was measured in plasma. TDF is converted to tenofovir in *vivo*. Tenofovir is subsequently phosphorylated intracellularly to its active moiety, tenofovir diphosphate. Therefore, the measurement of tenofovir in plasma, which serves as a surrogate for its intracellular form, is appropriate to assess pharmacokinetic parameters.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

In the original NDA submission formal PK/PD studies in adults to evaluate exposure-response were not performed. However, two studies conducted in treatment-experienced adults (GS-97-901 and GS-97-902) appear to support a dose-response relationship favoring the 300 mg once daily approved dosing regimen. Study 901 was a short-term, monotherapy, dose ranging study which demonstrated initial decreases in HIV-1 RNA were greater in the 300-mg dose treatment group as compared to the 75-mg and 150-mg treatment groups over 21 days. Further reductions in HIV-1 viral load were not seen for the 600-mg treatment group. Study 902, also demonstrated that reductions in HIV-1 RNA were greater for the 300-mg group compared to the 75-mg and 150-mg groups as part of combination therapy over 48 weeks of treatment. A 600-mg dose was not evaluated in this study.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

An exposure-response relationship for safety has not been identified for TDF. The two main safety concerns for TDF are renal toxicity and bone toxicity, including decreases in bone mineral density.

2.2.4.3 Are the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dosing regimen proposed for children 2 to < 12 years of age is supported by PK and efficacy data in adults as well as previous PK data from early studies conducted in the pediatric population (Study 926 and Study 927) which demonstrated that a dose of 8 mg/kg best matched

exposures achieved following a 300 mg dose in adults. There were potential concerns regarding adherence to the regimen due to the poor palatability of the TDF oral powder formulation, particularly in heavier patients requiring a larger amount of powder per dose. However, no association between amount of powder administered and exposures could be identified (i.e., subjects requiring larger amounts of TDF oral powder did not consistently have lower exposures when compared to subjects receiving smaller amounts of powder). Therefore, it could not be concluded that adherence would be an issue for this formulation. In addition, the introduction of the reduced-strength tablets for those patients who weight 17 to 35 kg and who are able to swallow an intact tablet should aid in addressing palatability issues.

2.2.5 What are the PK characteristics of tenofovir?

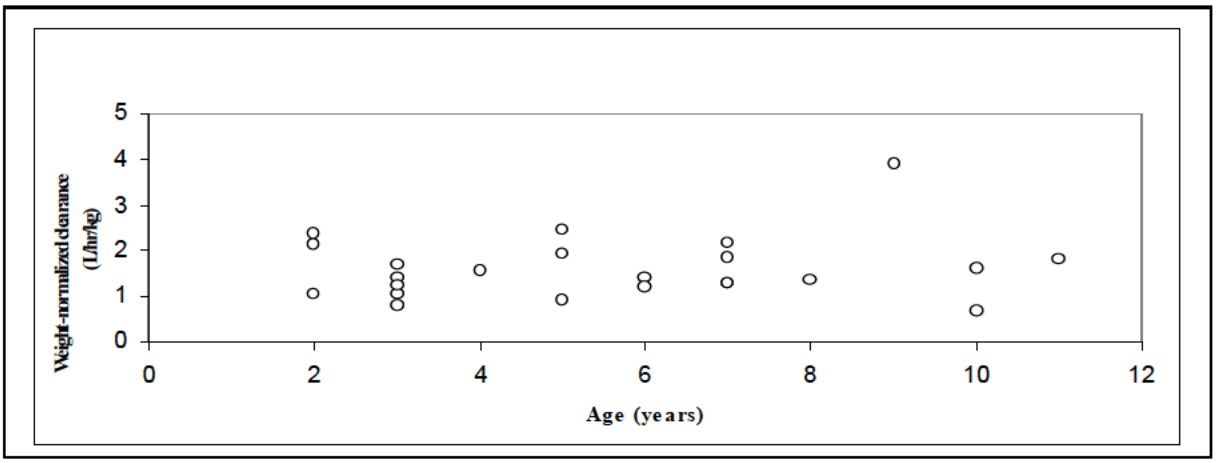
The PK of tenofovir is similar between healthy subjects and HIV-infected individuals, as well as between adults and adolescents. The PK is dose proportional over a dose range of 75 to 600 mg. There is minimal accumulation of tenofovir following multiple dosing. There is minimal metabolism of tenofovir and it is primarily eliminated through the kidney. Administration of TDF following a high-fat meal increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14% relative to fasting. However, administration of TDF with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. As shown in **Table 8**, AUC_{tau} in children following 4 weeks of dosing with 8 mg/kg/day of TDF oral powder approximated historical adult AUC_{tau} values (range 2742-3297 ng·h/mL) following 300 mg/day TDF dosing. **Figure 7** shows the weight-normalized clearance of tenofovir by age. The average age of subjects selected for the pediatric PK substudy was 6 years with an age range of 2 to 11 years. The overall mean of all subjects' ages in the main study was 7 years, with a range of 2 to 15 years. Mean body weight for subjects in the PK substudy was 21.2 kg while in the overall study it was 25 kg. Thus, subjects in the PK substudy are a fair demographic representation of the intended population in the overall study.

Table 8 – Mean Steady-State PK Parameters for Tenofovir in Children (GS-US-104-0352)

Tenofovir Plasma PK Parameter (Units)	Tenofovir 8 mg/kg in Subjects 2 to < 12 Years of Age (N = 23)
AUC_{tau} (ng•h/mL)[a] Mean (% CV)	2586.3 (40.9)
C_{max} (ng/mL) Mean (%CV)	238.7 (53.4)
C_{tau} (ng/mL)[a, b] Mean (%CV)	54.5 (43.4)
T_{max} (h) Median (Q1, Q3)	1.93 (1.08, 2.30)
$T_{1/2}$ (h)[a, c] Median (Q1, Q3)	13.65 (11.43, 16.00)

a Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour timepoint.

Figure 7 – Tenofovir weight-normalized clearance vs. age



2.3 Analytical

2.3.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tenofovir and the internal standard ([(b) (4)]) were resolved on a reverse phase HPLC and detected by a mass spec system (MS/MS). Quantitation of tenofovir is based on peak area ratio (tenofovir to [(b) (4)]) using a linear least squares regression with $1/concentration^2$ weighting. The calibration curve ranges from 10 to 1000 ng/mL and the limit of quantitation is 10 ng/mL tenofovir based on a 100 µL plasma sample.

2.3.2 Which metabolites have been selected for analysis and why?

Tenofovir was selected for quantitation for this study. TDF is converted to tenofovir in vivo. Tenofovir is then phosphorylated intracellularly to its active moiety, tenofovir disphosphate. Thus, the measurement of tenofovir in plasma is an appropriate surrogate for its intracellular form. No metabolites of tenofovir were selected for measurement.

2.3.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Tenofovir was measured in its total form. Tenofovir exists as approximately 93% unbound in plasma. Thus in this case, the distinction between the measurement of free or total drug is virtually inconsequential since almost the entire drug is unbound in plasma.

2.3.4 What bioanalytical methods are used to assess concentrations?

Tenofovir and the internal standard ([(b) (4)]) were resolved on a reverse phase HPLC and detected by a mass spec system (MS/MS). The quantitation of tenofovir was based on the ratio of the peak areas of tenofovir to [(b) (4)] within each run. The quantification of tenofovir has been validated in the range of [(b) (4)] ng/mL using a sample volume of 0.10 mL. **Table 9** displays the key pre-study method validation data based on QC samples prepared at 4 different concentrations and run in replicates of 5 with each of 3 runs.

Table 9 – Assay Validation Precision and Accuracy

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-assay	Inter-assay
Tenofovir	(b) (4)% to (b) (4)%	(b) (4)% to (b) (4)%	(b) (4)% to (b) (4)%	(b) (4)% to (b) (4)%

* Precision is expressed as % relative standard deviation (% RSD)
** Accuracy is expressed as % bias (mean percent difference from nominal concentration)

The percent accuracy for the calibration standards (concentration range: (b) (4) ng/mL) ranged from (b) (4)% to (b) (4)%. The precision range was (b) (4)%. These values are within an acceptable range. The correlation coefficient for the calibration curve was >0.99 in all validation runs. Specificity of the method was demonstrated using blank plasma samples. Stability assessments included demonstration of bench-top stability at room temperature for 24 hours, autosampler stability at 4˚C for 5 days, freeze/thaw stability (3 cycles) at -80˚C, and long-term storage stability at -80˚C for 460. An updated version (v9) of the method validation report provides partial validation data supporting long-term storage stability at -80˚C for 1426 days.

The analytical performance for Study 0352 and 0312 is summarized in the individual study review (See Section 4).

3 DETAILED LABELING RECOMMENDATIONS

Labeling statements for NDA 22-577 and NDA 21-356 S-038 to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underlined blue font.

HIGHLIGHTS OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

(b) (4)

(b) (4)

Reviewer comment: Under section 8.3 Nursing Mothers, the Sponsor has proposed to insert the following language: (b) (4)

(b) (4)

Under Section 12.3 Pharmacokinetics: Effects of Food on Oral Absorption, the words "300 mg tablet" were inserted into the sentence "Administration of VIREAD 300 mg tablet following a high-fat meal…" to provide clarification that an effect of food has been seen for the VIREAD tablet formulation only. Food effect studies have not been conducted for the VIREAD oral powder formulation.

4 INDIVIDUAL STUDY SYNOPSIS

4.1 Individual Study Review

4.1.1 GS-US-104-0352

Title
"A Phase 3, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy"

Information Regarding the Clinical Study Sites
This trial enrolled subjects at 9 study sites: 6 in the US, 1 in Panama, and 2 in the UK.

Objectives
The primary objective of this study (Weeks 0-48) was as follows:

- To assess the efficacy of switching to tenofovir DF compared to continuing stavudine or zidovudine in maintaining virologic suppression (plasma HIV-1 ribonucleic acid [RNA] <400 copies/mL) in HIV-1 infected children at Week 48

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of tenofovir DF in HIV-1 infected children
- To evaluate the effects of switching from stavudine or zidovudine to tenofovir DF versus continuing stavudine or zidovudine on bone mineral density, fasting lipid parameters and fat distribution
- To evaluate the pharmacokinetics of tenofovir in a subset of HIV-1 infected children receiving tenofovir DF oral powder formulation

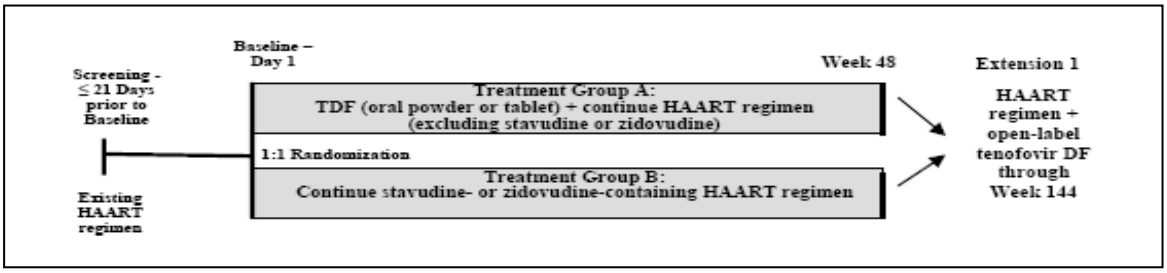
- To evaluate the long-term efficacy, safety, and tolerability of treatment with tenofovir DF through up to 144 weeks of drug exposure

Study Design

The first 48 weeks of this study was a randomized, open-label, parallel-group treatment period evaluating the safety, efficacy, and tolerability of TDF in children ages 2 to <12 years. Subjects were randomized 1:1 to either replace stavudine or zidovudine with tenofovir DF (Treatment Group A) or continue stavudine or zidovudine (Treatment Group B) in their current anti-retroviral regimen. Randomization was stratified by whether a subject was currently on stavudine or zidovudine. A sample size of one-hundred evaluable subjects (50 per treatment arm) was planned for this study. The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA levels < 400 copies/mL at Week 48. Secondary efficacy endpoints included the proportion of subjects with HIV-1 RNA < 50 copies/mL and change from baseline in CD4 cell count and CD4 percentage.

After completing 48 weeks of treatment in their assigned treatment groups, eligible subjects from both treatment groups were given the option to continue (or initiate) treatment with TDF in two 96-week study extension periods. Subjects initially randomized to Treatment Group B were switched from stavudine or zidovudine to TDF in the study extension if the investigator determined that TDF would be safe and beneficial for the subject. The figure below displays the design schema for Study 0352.

Study 0352 Schema



Safety data was collected in the randomization phase and extension phases for the following parameters: adverse events; clinical laboratory tests; spine and total body BMD and limb, trunk, and total body fat (assessed using DEXA); bone biochemical markers; height; weight; vital signs; physical examinations (complete or symptom-directed), and changes from baseline in fasting lipid parameters.

PK samples were taken from a subset of 23 subjects who received at least 4 weeks of TDF oral powder at a dose of approximately 8 mg/kg once daily. On the day of PK sampling the dose was to be administered following a meal (meal type was not specified). The following steady-state PK parameters of tenofovir in plasma were evaluated: C_{max}, C_{max}/dose, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z(Kel), $T_{1/2}$, AUC_{tau}, AUC_{tau}/dose, $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}$/dose, and CL/F. PK sampling occurred over a period of 12 hours and specimens were drawn at the following time points: 0, 1, 2, 4, 8, and 12 hours after TDF dosing.

Key Inclusion Criteria

- 2 to <12 years of age
- HIV-1 RNA < 400 copies/mL
- Naïve to tenofovir DF

- Treatment-experienced and on a stable stavudine- or zidovudine-containing antiretroviral regimen for at least 12 weeks prior to study entry
- ALT and ALT values ≤ 3 X ULN
- Estimated creatinine clearance ≥ 80 mL/min/1.73m^2 (using Schwartz Formula)
- Adequate renal function: Subjects were required to have a serum creatinine value at, or below the maximum serum creatinine values below:

Age (Years)	Maximum Serum Creatinine (mg/dL)
≥ 2 to < 5	0.8
≥ 5 to < 10	1.0
≥ 10 to ≤ 15	1.2

Key Exclusion Criteria

- Received didanosine as part of their background regimen
- Pregnant or lactating subjects
- Needed ongoing therapy with any of the following:
  - nephrotoxic agents
  - systemic chemotherapeutic agents
  - systemic corticosteroids (short courses <2 weeks were allowable)
  - interleukin-2 (IL-2) and other immunomodulating agents
  - investigational agents (except with the expressed approval of the sponsor)
- Prior history of significant renal disease (i.e., nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis)
- Prior history of significant bone disease (i.e., osteomalacia, chronic osteomyelitis, osteogenesis imperfecta, osteochondroses, multiple bone fractures)

Formulation(s) Used

- TDF oral powder (40 mg/1 gm) – used in subjects who weighed ≤ 37 kg or were unable to swallow the TDF tablet
- Marketed TDF 300 mg tablet – used in subjects who weighed > 37 kg and who were able to swallow an intact tablet

Dosage and Administration

In this study 40 subjects in the TDF treatment arm received the oral powder formulation, 5 subjects received the tablet formulation, and 3 subjects received both formulations over the course of the 48 weeks. Subjects receiving the tablet were given one 300-mg tenofovir DF tablet per day, followed by 240 mL (8 fluid ounces) of water. Subjects could take their daily dose with or without food. Subjects receiving the oral powder received a dose of 8 mg/kg, once daily, up to a maximum dose of 300 mg. The dosing tablet used in the study is consistent with the final dosing table proposed for the label, including the same weight bands and with doses rounded to the nearest 20 mg (half-scoop). The subject's dose of tenofovir DF oral powder was mixed with 2–4 ounces of applesauce or an equivalent food (i.e., a food that did not require chewing) in a plastic cup or bowl without grooves. After the subject consumed the applesauce (or equivalent), 120 mL of water (4 fluid ounces) was added and swirled within the bowl to suspend all residual food and powder. Subjects were then instructed to drink the water-food mixture followed by an additional 120 mL of water (total of 240 mL or 8 fluid ounces). All subjects who initiated the oral powder were to continue receiving the oral powder through Week 48.

Rationale for Dose selection

The basis for dose selection in the pediatric study was to target effective adult exposures achieved following administration of TDF 300 mg once daily (approved adult regimen). Two early phase single- and multi-dose pediatric PK studies (GS-01-926 and GS-01-927) explored TDF doses of 3 to 10 mg/kg in children ages 6-16 years old (12 subjects were less than 12 years of age) and demonstrated that tenofovir exposures achieved following a TDF dose of 8 mg/kg in children best matched adult exposures achieved following a 300 mg TDF dose.

Statistical Methods

Efficacy

The ITT analysis set was the primary efficacy analysis set and included subjects who were randomized, received at lease one dose of study medication, and did not violate any major study entry criteria. The primary efficacy endpoint, the proportion of subjects with HIV-1 RNA < 400 copies/mL, was compared between the two treatment groups. The pre-specified primary analysis included a two-sided 95% confidence interval constructed about the difference in response rates between the two groups based on normal approximation methods for a binominal distribution. Treatment noninferiority was determined if the lower confidence bound of the difference between treatment groups was greater than -0.15. P-values were provided using Fisher's exact test.

Descriptive summaries for the All TDF group (including extension phase data) were provided for all secondary efficacy endpoints. The secondary efficacy endpoints were analyzed as follows:

The proportion of subjects with HIV-1 RNA < 50 copies/mL was analyzed in the same manner as the primary endpoint. Results of the primary analysis of this secondary efficacy endpoint were confirmed using the ITT analysis set excluding those subjects with HIV-1 RNA > 50 copies/mL at baseline.

The baseline value and change from baseline by visit in CD4 cell count and CD4 cell percentage were summarized. A two-sided 95% CI was constructed about the difference in mean baseline values and changes from baseline CD4 cell count and CD4 cell percentage between the two treatment groups (tenofovir DF group minus stavudine or zidovudine group). P-values from a Wilcoxon rank sum test were provided to test for differences between randomized treatment groups.

Safety

The RAT analysis set (i.e., subjects who were randomized into the study and received at least one dose of study medication) was the primary analysis set for safety.

Clinical laboratory tests were graded according to the Gilead Sciences, Inc. (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. Treatment-emergent laboratory abnormalities and marked abnormalities were summarized by maximum post-baseline toxicity grade. Baseline values and changes from baseline in laboratory measurements, including chemistry, hematology, bone biochemical markers, and fasting lipids were descriptively summarized by visit and treatment group. Between group differences for bone biochemical markers and fasting lipid parameters were tested using a Wilcoxon rank sum test.

Changes from baseline in BMD and fat distribution (limb fat, trunk fat, and total body fat) were also summarized by visit and treatment group.

Baseline values and changes from baseline in fat distribution, baseline BMD values, and percent change from baseline in spine and total body BMD were summarized. For these endpoints, treatment group differences were tested using a Wilcoxon rank sum test. Spine and total body BMD, and body weight and height Z-scores and changes from baseline in Z-scores were descriptively summarized.

Pharmacokinetics

The steady-state pharmacokinetic parameters (C_{max}, C_{max}/dose, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z (Kel), $T_{½}$, AUC_{tau}, AUC_{tau}/dose; $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}$/dose, and CL/F) of tenofovir in plasma were estimated using noncompartmental analysis in WinNonlin® software (Version 5.2, Pharsight Corporation, USA). The linear/log trapezoidal rule was used in conjunction with an extravascular input model, with input values for dose, time of dose, plasma concentration, and corresponding real-time values based on drug dosing times whenever possible.

Predose sample times were assigned a time value of zero. The nominal time point for the dosing interval (tau) was used for calculation of AUC over this specific dose interval. The predose concentration was used as a surrogate for the concentration at 24 hours.

Pharmacokinetic analyses were performed using the PK analysis set. Pharmacokinetic parameters were derived by a GSI pharmacokinetic scientist, and were listed and summarized using descriptive statistics. Plasma tenofovir concentrations (ng/mL) were listed for each subject and summarized by sampling time point using descriptive statistics. Figures for mean (SD) and median (Q1, Q3) plasma concentrations of tenofovir against sampling time point after dosing were generated using linear and log/linear scales.

Plasma concentrations and PK parameters were both summarized by age group (2 to < 6 years and 6 to < 12 years) and overall (2 to < 12 years).

Bioanalytical Methods

The method and bioanalysis of tenofovir is acceptable. Concentrations of tenofovir in plasma samples collected during the PK substudy were determined using Good Laboratory Practice (GLP) methods and validated liquid chromatography-tandem mass spectroscopy (LC/MS/MS) bioanalytical methods. The assays were performed by Gilead Sciences Bioanalytical Laboratory (Durham, NC). All samples were analyzed in the timeframe supported by frozen stability storage data. The long-term stability data for tenofovir of 1426 days (at -80˚C) covers the duration of long term stability data necessary for the 0352 trial.

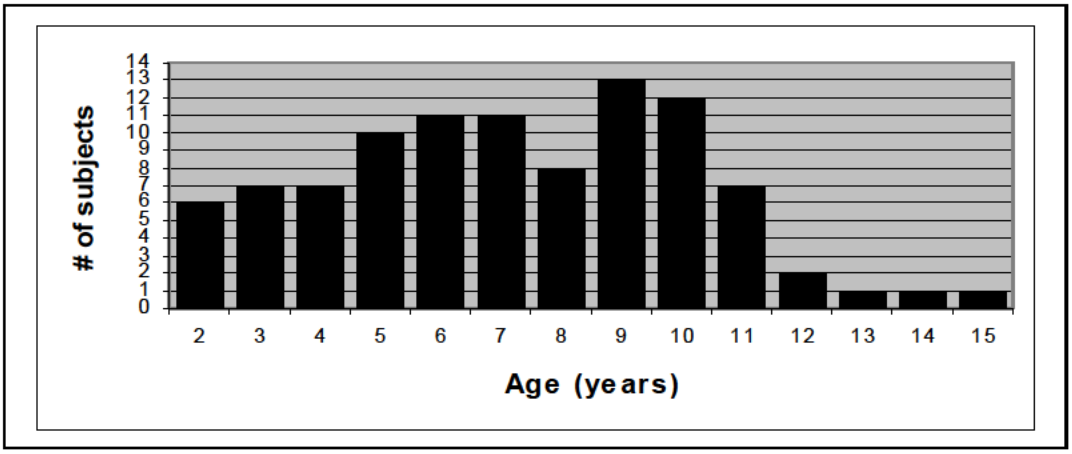
For tenofovir the lower limit of quantification was 10 ng/mL and the upper limit of quantification was 1000 ng/mL. Calibration curves were obtained using a liner regression algorithm with 1/concentration weighting of the peak area ration of tenofovir to internal standard versus concentration. All correlations coefficients (r) were greater than 0.99. Study samples were analyzed in 4 separate runs between March 19 and September 3, 2008. Each analytical run met the pre-specified acceptance criteria. A minimum of 6 QC samples were analyzed with each analytical run. Inter-assay precision ranged from 4.0 to 9.9% and accuracy ranged from -4.4 to 4.6%.

Results

This was a multicenter and multinational study with a total of 9 clinical sites which included 6 sites in the U.S., 1 site in Panama, and 2 sites in the U.K.

The following figure shows the age distribution of subjects included in Study 0352.

Study 0352 Age Distribution



Efficacy

A total of 97 subjects were randomized in this study (48 in the TDF treatment arm, 49 in the stavudine or zidovudine treatment arm). At Week 48, the proportion of subjects with HIV-1 RNA <400 copies/mL was 83% for the TDF treatment group and 92% for the stavudine or zidovudine treatment group. The difference in response rates between the treatment groups failed to meet the noninferiority margin of the lower confidence bound being greater than –0.15. However, in a post-hoc analysis which looked at the virologic endpoint over a defined window of time, 87.5% of subjects in the TDF treatment group and 87.8% in the stavudine or zidovudine treatment group achieved a viral load of <400 copies/mL at Week 48. This difference in response rates between the treatment groups met the noninferiority margin.

Safety

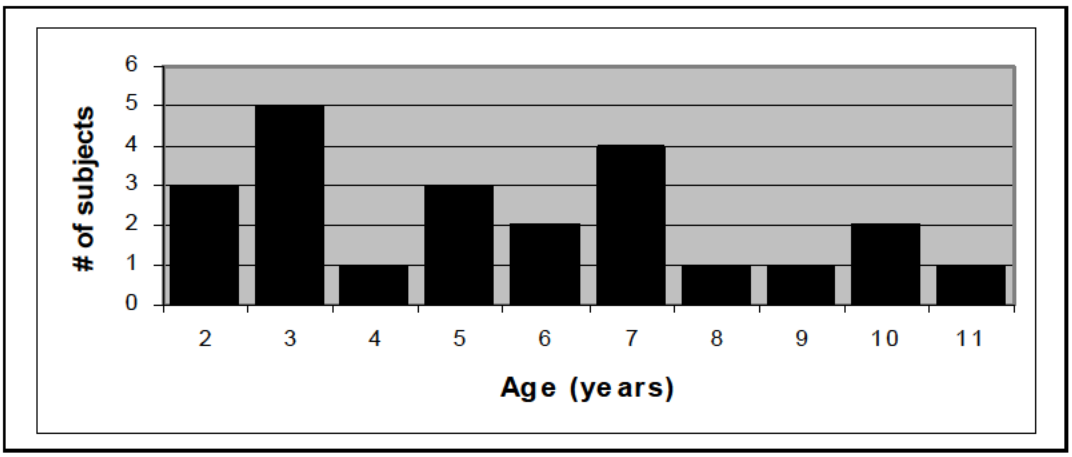
The safety findings in the pediatric study were consistent with that seen in adult studies of TDF. The most common categories of treatment-emergent adverse events reported, by system organ class, were infections and infestations, gastrointestinal, respiratory, and skin disorders. The most frequently reported treatment-emergent nasopharyngitis (31%) and cough (11%). TDF had negative effects on total bone mineral density and renal function similar to what was seen in the adults and adolescents.

Pharmacokinetics

Twenty-three subjects completed the PK substudy. All subjects enrolled in the PK substudy were from the Panama clinical site. The average age of subjects selected for the pediatric PK substudy was 6 years with an age range of 2 to 11 years. The overall mean of all subjects' ages in the main study was 7 years, with a range of 2 to 15 years. Mean weight for subjects in the PK substudy was 21.2 kg while in the overall study it was 25 kg. Thus, subjects in the PK substudy are a fair demographic representation of the intended population in the overall study.

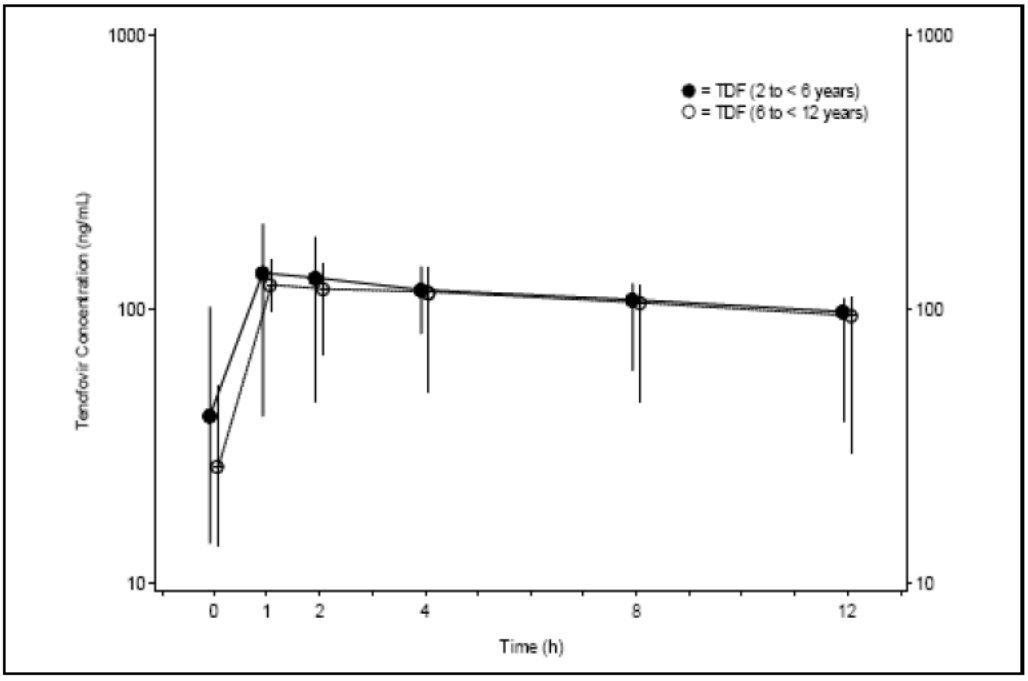
The following figure shows the age distribution of subjects included in the PK substudy of Study 0352.

Study 0352 PK Substudy Age Distribution



The figure below represents the mean concentration vs. time profile for subjects in the PK subset by age group.

Mean Steady-State Plasma Concentrations of Tenofovir (log-linear)



Tenofovir pharmacokinetics following administration of the oral powder formulation of TDF at a dose of 8 mg/kg daily under steady-state conditions in HIV-1 infected children (2 to <12 years) over all and by age group are presented in the table below.

Steady-State Pharmacokinetic Parameters for Tenofovir Overall and by Age Group

TFV Plasma PK Parameter (Units)	Tenofovir DF 8 mg/kg		
	Overall (N = 23)	2 to < 6 years (N = 12)	6 to < 12 years (N = 11)
AUC_{tau} (ng•h/mL)[a] Mean (% CV)	2586.3 (40.9)	2679.1 (39.9)	2485.0 (43.8)
AUC_{last} (ng•h/mL) Mean (% CV)	1704.4 (42.9)	1780.6 (43.5)	1621.3 (43.8)
C_{max} (ng/mL) Mean (%CV)	238.7 (53.4)	257.2 (58.9)	218.5 (44.8)
C_{tau} (ng/mL)[a, b] Mean (%CV)	54.5 (43.4)	55.4 (47.3)	53.4 (41.0)
CL/F (L/h)[a] Mean (%CV)	34.7 (71.4)	22.7 (40.6)	47.8 (62.5)
T_{max} (h) Median (Q1, Q3)	1.93 (1.08, 2.30)	1.98 (1.20, 2.24)	1.22 (1.00, 4.00)
T_{last} (h) Median (Q1, Q3)	12.00 (12.00, 12.00)	12.00 (12.00, 12.05)	12.00 (12.00, 12.00)
$T_{½}$ (h)[a, c] Median (Q1, Q3)	13.65 (11.43, 16.00)	13.85 (9.96, 16.54)	12.31 (11.43, 15.99)

a Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour timepoint.

For comparison, the following table summarizes historical steady-state tenofovir PK parameters observed at varying time points in HIV-1 infected adults (Studies GS-97-901 and GS-99-907).

Historical Steady-State Tenofovir PK Parameters in HIV-1 Infected Adults

TFV Plasma PK Parameter (Units)	GS-97-901 300 mg/day		GS-99-907 300 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) Mean (% CV)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{tau} (ng/mL) Mean (%CV)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	3.0	2.3	2.3	2.3	1.5	2.5
$T_{½}$ (h) Median (Q1, Q3)	13.7	14.4	14.0	14.9	12.4	14.5

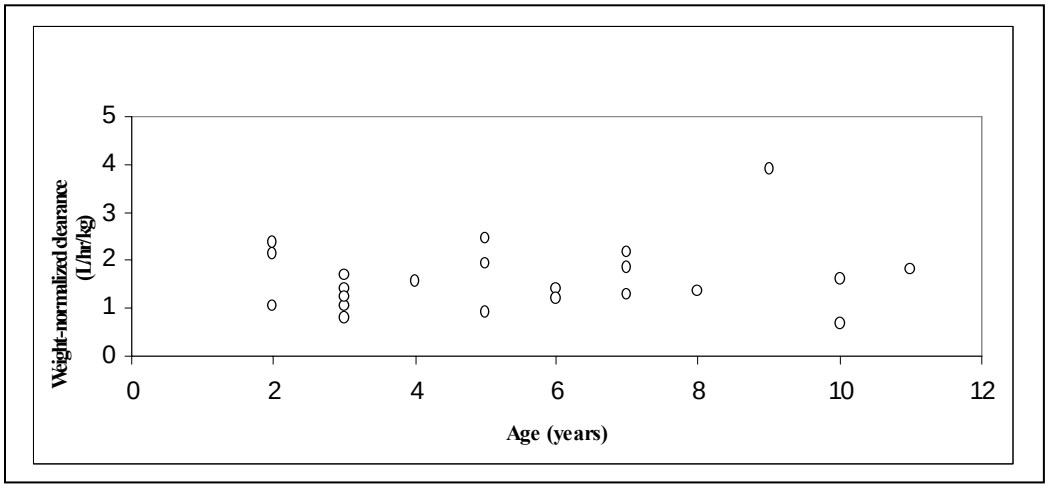
Tenofovir exposures in the pediatric PK substudy were similar to those achieved following administration of TDF 300 mg tablets in HIV-1 infected adults.

Reviewer Comment: In the PK substudy of study 0352, a dose of 8 mg/kg TDF oral powder once daily for 4 weeks yielded mean steady-state exposures in children 2 to <6 years and 6 to <12 years of age that were lower by 11% and 18%, respectively, when compared to historical mean steady-state exposures observed in adults who were administered TDF 300 mg once daily for 4 weeks. When investigating the differences in exposures between the two age cohorts, an outlier (Subject 9050 – a 9 y/o male with an individual AUC_{tau} value over 2.5 times lower than the mean AUC for the cohort) was identified in the pediatric PK dataset. Removal of this subject from the dataset resulted in the difference in mean AUC_{tau} between children 6 to <12 years and adults to become approximately 12%. Furthermore, when comparing overall exposures in children 2 to <12 years to the lower end of the range of steady-state exposures observed in adult historical data (AUC_{tau}: 2742-3297 ng·h/mL), the difference in mean exposures between children and adults was reduced to 3%. It should also be noted that protocols for historical PK studies conducted in adults specified that TDF was to be administered following a high-fat meal, while the pediatric PK study protocol did not specify a meal type. There is a known food-effect for TDF. Administration of TDF following a high-fat meal increases tenofovir AUC and C_{max} by approximately 40% and 14%, respectively. The difference in administration of TDF in the PK study in adults and children may have contribution toward the difference in tenofovir exposures.

Nonetheless, the difference in mean AUC_{tau} values between adults and pediatric is small and would not be expected to result in a clinically significant shift in efficacy. When subjects in the pediatric PK substudy were broken down into 3 groups based on exposures (high, mid, low) there was no clear correlation between AUC value and clinical outcome. In addition, of the 19 virologic failures in study 0352, no cases of tenofovir resistance were identified. This is indicative that children in this study were not exposed to suboptimal doses of TDF for prolonged periods of time. (It should be noted that one subject, Subject 9093, in the TDF treatment group had an increase in viral load early in the study and was discontinued from the study at Week 4. Genotyping of a plasma sample from this subject revealed HIV RT mutations K65R and Y181C. This rapid detection of HIV resistance mutations by Week 4 was more likely indicative of preexisting resistance at study entry than suboptimal exposures). Thus, the totality of the pharmacokinetic data supports dosing in children 2 to < 12 years of age at a dose of TDF 8 mg/kg (up to maximum of 300 mg) once daily.

The figure below represents the weight-normalized tenofovir clearance by age in the pediatric PK substudy.

Weight-Normalized Tenofovir Clearance vs. Age



Reviewer Note: In subjects 2 to < 12 years of age tenofovir clearance is similar when normalize for weight. This provides further support for the conclusion that it is appropriate to recommend the same mg/kg dose of TDF across this age range.

Inspection Results

The Office of Scientific Investigations was requested to conduct inspections of the clinical site where the PK substudy was conducted (Clinical Site# 1578, Panama City, Panama) and of the bioanalytical laboratory that analyzed the tenofovir plasma samples (Gilead Sciences, Inc., Durham, NC). Following these inspections, no significant objectionable conditions were observed and Form FDA-483 was not issued. The OSI Reviewer concluded that the PK data from the clinical and bioanalytical portions of the study are acceptable for Agency review (see DSI Consult – Bioequivalence Establishment Inspection Report Review).

Conclusion

Tenofovir pharmacokinetics following the administration of the oral powder formulation of TDF at a dose of 8 mg/kg/day in HIV-1 infected children ages 2 to < 12 years of age is similar to that achieved following administration of TDF 300 mg tablets in HIV-1 infected adults, and thus confirms the appropriateness of this dose in this age range.

4.1.2 GS-US-104-0312

Title

"A Phase 1 Pharmacokinetic Study to Evaluate the Relative Bioavailability and Bioequivalence Between Tenofovir Disoproxil Fumarate (Tenofovir DF) Oral Powder and Tablet Formulations"

Information Regarding the Clinical Study Site

This study was conduced at one site in the US (Comprehensive Clinical Development, formerly known as Northwest Kinetics, Inc., Tacoma, WA)

Objectives

The primary objective of this study was as follows:

- Determine the relative bioavailability between the investigational oral powder and 300 mg tablet formulation of tenofovir DF

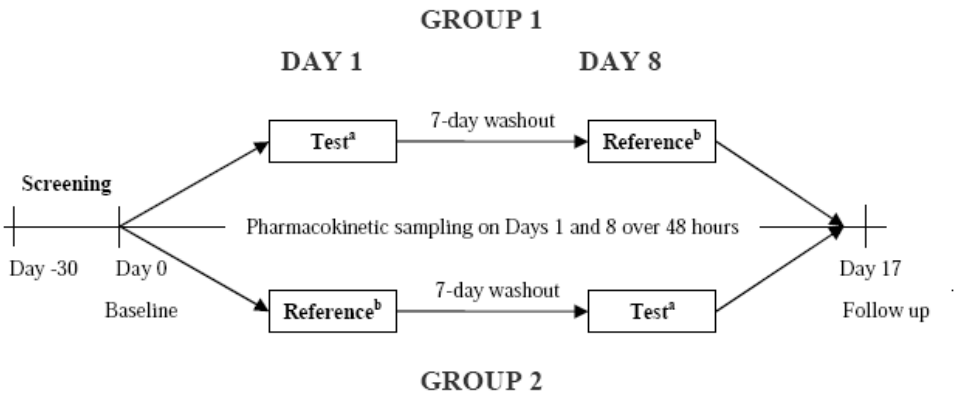
The secondary objectives of this study were as follows:

- Evaluate the bioequivalence between the investigational oral powder and 300 mg tablet formulation of tenofovir DF
- Assess the safety of the tenofovir DF oral powder formulation

Study Design

GS-US-104-0312 was a Phase 1, open label, randomized, two-way crossover, single dose PK study that enrolled healthy male and female subjects between the ages of 18 to 45 years old. A total of 32 subjects (16 per treatment arm) were planned for this study. Subjects were randomized to either Group 1 (oral powder formulation followed by tablet formulation) or Group 2 (tablet formulation followed by oral powder formulation). All subjects fasted overnight on Days 0 and 7, and received study medication on the mornings of Days 1 and 8. A 300 mg dose of the powder formulation was administered orally mixed in 4 ounces of applesauce followed by 240 mL of water. The 300 mg tablet formulation was administered orally with 240 mL of water and within 5 minutes of consuming 4 ounces of applesauce. A 7-day washout period was provided between each treatment. A schema of the trial design is displayed in the figure below.

Study 0312 Schema



PK blood sampling took place over a 48-hour period after dosing on Days 1 and 8. Blood samples were collected at the following time points: predose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours after dosing. The following PK parameters were determined for tenofovir from oral powder and tablet formulations of tenofovir DF: C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $AUC_{0\text{-}last}$, AUC_{inf}, % AUC_{exp}, $T_{1/2}$, V_z/F, and CL/F. Subjects were required to remain in the study facility overnight from Day 0 through Day 3 (48 hours post dose) and from Day 7 through Day 10 (48 hours post dose).

Safety was assessed throughout the study by evaluation of clinical laboratory tests, weight, vital signs, periodic physical examinations, and monitoring of adverse events (AEs) and concomitant medications. Subjects were contacted by telephone on Day 17 for follow up regarding if they had experienced any adverse events.

Key Inclusion Criteria

- 18 to 45 years of age inclusive
- In good health based upon medical history, physical exam, and clinical laboratory test results
- Negative serum pregnancy test (for females)

Key Exclusion Criteria

- Received any medication, including over-the-counter medications or herbal products within 2 weeks of commencing study drug dosing, with the exception of vitamins and/or acetaminophen (ibuprofen was not allowed) and/or hormone contraceptive (oral, implant, patch, or injections) including Depo-Provera®
- Received therapy with nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, tacrolimus, or cyclosporine) or potential competitors of renal excretion (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, probenecid, or high-dose nonsteroidal anti-inflammatory drugs [i.e., ibuprofen]) within 3 months of study screening, or was expected to receive these during the study
- Pregnant or lactating females
- Alcohol or illicit drug abuse

Formulation(s) Used

TDF oral powder (40mg/1gm); TDF tablet (300 mg)

Statistical Methods

Pharmacokinetics
For tenofovir, the primary pharmacokinetic parameters $AUC_{0\text{-last}}$, AUC_{inf}, and C_{max} were analyzed untransformed and natural-log transformed. These parameters were compared by analysis of variance (ANOVA). The statistical model included the sequence, dosing period, and treatment as fixed effects, and subject as a random effect. From this ANOVA model, 90% confidence intervals (CIs) were obtained for the geometric least-squares mean ratios of oral powder formulation (Test Treatment) versus tablet formulation (Reference Treatment) for the respective pharmacokinetic parameters. The relative bioavailability between the oral powder and tablet formulations was estimated based on the geometric least-squares mean ratio of AUC_{inf}. Bioequivalence was concluded if 90% CIs for $AUC_{0\text{-last}}$, AUC_{inf}, and C_{max} fell within 80% to 125%.

Bioanalytical Methods

The methods and bioanalysis of tenofovir are acceptable. Concentrations of tenofovir in human plasma samples collected during the pharmacokinetic study were determined using liquid chromatography/tandem mass spectrometry (LC/MS/MS) bioanalytical assays. The assay for tenofovir was validated by Gilead Sciences Bioanalytical Laboratory (Durham, NC, USA).

For the in-study validation, routine study samples were analyzed along with sixteen calibration standards and at least six QC samples per analytical run. All correlation coefficients (r) exceeded 0.99. The inter-day precision ranged from 7.3% to 9.0% and inter-day accuracy ranged from -2.0% to 4.4%.

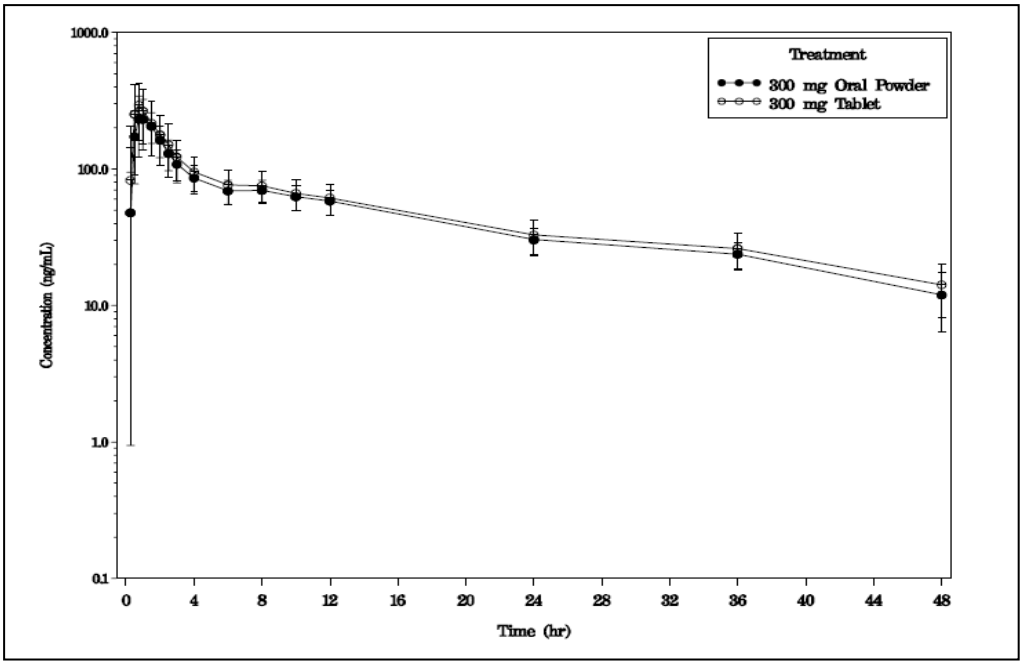
The long term stability of tenofovir in human plasma stored at -80°C for 460 days was determined to be acceptable using quality control samples. The study samples were stored for a maximum of 119 days. The long-term storage stability data is acceptable.

Safety
Adverse events, laboratory data, vital signs, weight, physical examination results, and concomitant medications were listed and summarized for all subjects (including change from predose in each treatment period), as appropriate.

Results
A total of 32 subjects were randomized and treated in this study, with 30 subjects completing both treatment periods (2 subjects withdrew consent on Day 1). In the pharmacokinetic analysis set, 80% of subjects were white, 10% were black, 7% were Asian, and 3% were native Hawaiian or Pacific Islander. The majority of subjects (63%) were male. The mean age was 26 years, mean weight at screening was 71.4 kg, mean height was 173.4 cm, mean BMI was 23.7 kg/m^2, and the mean estimated creatinine clearance was 122.4 mL/min. The safety analysis set had a similar demographic profile and baseline characteristics as the pharmacokinetic analysis set.

Pharmacokinetics
The figure below displays the mean plasma tenofovir concentration-time profile for the oral powder and tablet formulations.

Mean and Standard Deviation of Plasma Tenofovir Concentration-Time Profile



Geometric least-squares mean ratios for tenofovir from tenofovir DF oral powder formulation compared to tenofovir DF tablet formulation were 73% for C_{max}, 93% for $AUC_{0\text{-}last}$, and 92% for AUC_{inf} (as summarized in the table below). The 90% CIs for the geometric mean ratios were contained within the equivalence bounds of 80% to 125% for $AUC_{0\text{-}last}$ and AUC_{inf}, but not for C_{max} (lower bound 66%).

Statistical Comparisons of Tenofovir PK Parameters for Oral Powder vs. Tablet Formulations

Tenofovir Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		Geometric Least Squares Mean Ratio (%)	90% CI
	Tenofovir DF Oral Powder 300 mg (N = 30)	Tenofovir DF Tablet 300 mg (N = 30)		
C_{max} (ng/mL)	258.27	353.39	73.08	66.04, 80.88
$AUC_{0\text{-}last}$ (h•ng/mL)	2106.22	2262.15	93.11	83.39, 103.96
AUC_{inf} (h•ng/mL)	2486.18	2706.66	91.85	83.37, 101.21

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on the natural logarithmic scale.

Reviewer Note: Tenofovir Cmax was 27% lower following administration of the TDF oral powder relative to the tablet formulation. This difference in Cmax is likely explained by a slower absorption of the oral powder due to the granule-encapsulating coating that surrounds the powder for taste masking. While the 90% CI of the geometric mean ratios for Cmax were not contained within 80% to 125%, the formulations performed similarly in terms of $AUC_{0\text{-}last}$ and AUC_{inf}. In terms of clinical efficacy, AUC is the more pertinent parameter of exposure for this class of drugs (nucleotide reverse transcriptase inhibitors). Therefore, this difference in Cmax

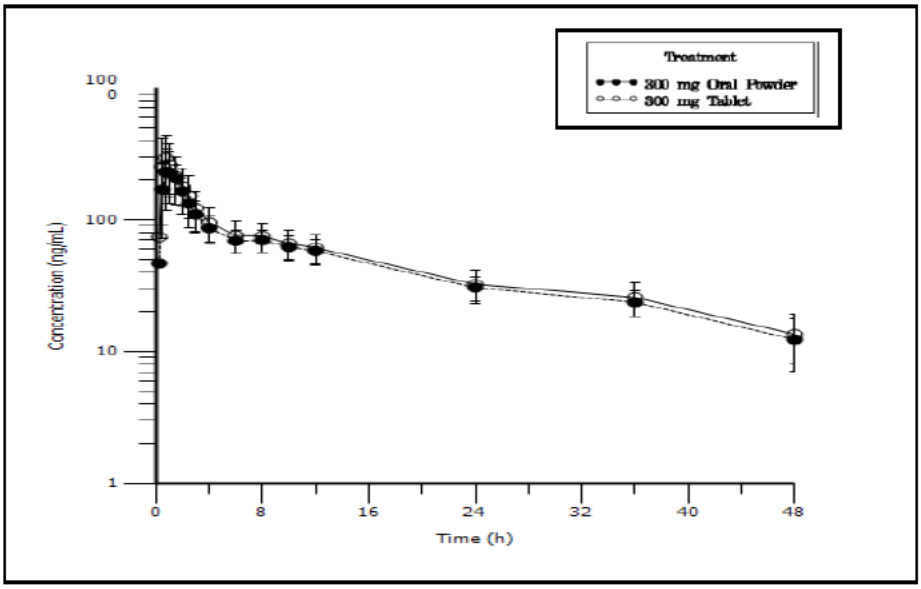
between the two formulations is not considered clinically relevant.

Inspection Results

The Office of Scientific Investigations was requested to conduct inspections of the clinical site where the BE study was performed (Comprehensive Clinical Development, Tacoma, WA) and the bioanalytical laboratory that analyzed the tenofovir plasma samples (Gilead Sciences, Inc., Durham, NC). Following these inspections, form FDA-483 was issued at both sites. It was ultimately concluded by the OSI Reviewer that the data from the clinical portion of Study 0312 are acceptable for Agency review. However, in terms of the analytical portion of the study, it was determined that the accuracy of pharmacokinetic measurements for two subjects in the study (subjects 20 and 21 – whose samples were re-injected multiple times) could not be assured due to failure of the site to conduct a re-injection reproducibility experiment during pre-study method validation for the tenofovir LC-MS/MS method. Therefore, it was concluded by the OSI Reviewer that the data for subjects 20 and 21 should be excluded from the bioequivalence assessment (see DSI Consult – Bioequivalence Establishment Inspection Report Review).

Reviewer note: A re-analysis of the data obtained from Study 0312 was performed by this Reviewer following the removal of subjects 20 and 21 from the dataset. The mean and standard deviation of plasma tenofovir concentration-time profiles for the oral powder and tablet formulations are displayed in the figure below.

Mean and Standard Deviation of Plasma Tenofovir Concentration-Time Profiles for Oral Powder and Tablet Formulations (Re-analysis following removal of subjects 20 and 21 from the dataset)



The table below provides a summary of tenofovir pharmacokinetic parameters following administration of the TDF oral powder and tablet formulations.

Summary of Tenofovir PK Parameters (Re-analysis following removal of subjects 20 and

21 from dataset)

Tenofovir Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		Geometric Least Squares Mean Ratio (%)	90% CI
	Tenofovir DF Oral Powder 300 mg (N=28)	Tenofovir DF Tablet 300 mg (N=28)		
C_{max} (ng/mL)	257.29	347.52	74.04	66.50, 82.43
$AUC_{0\text{-}last}$ (h•ng/mL)	2146.61	2270.13	94.56	84.15, 106.26
AUC_{inf} (h•ng/mL)	2512.01	2657.10	94.54	84.72, 105.49

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on the natural logarithmic scale.

Reviewer comment (cont.): The removal of subjects 20 and 21 from the dataset did not result in a significant change to the results of the study (tenofovir C_{max} is now 26% lower as opposed to 27% lower following administration of the oral powder formulation compared to the tablet formulation) and did not change the conclusion of the study (the 90% CIs for the GMR for $AUC_{0\text{-}last}$ and AUC_{inf} were contained within 80%-125%, however the 90% CIs for the GMR for C_{max} were not).

Safety

There were no deaths or serious AEs, and no subjects discontinued the study due to AEs. Treatment-emergent AEs were reported for 18 of 32 subjects (56%, 47 events) overall; 12 of 30 subjects (40%, 18 events) after administration of the tenofovir DF oral powder formulation compared with 15 of 32 subjects (47%, 29 events) after administration of the tenofovir DF tablet formulation. All treatment-emergent AEs were Grade 1 in severity, and all resolved. AEs considered by the investigator to be related to study drug were reported for three subjects after administration of the tenofovir DF oral powder formulation (four events: flatulence in two subjects, and hot flush and increased alanine aminotransferase each in one subject); no AEs were considered related to study drug after administration of the tenofovir DF tablet formulation. Overall, there were no clinically relevant changes from pre- to post-dose for clinical laboratory parameters, vital signs, or body weight.

Conclusion

Tenofovir mean C_{max} values were 26% lower following administration of the oral powder formulation compared to the tablet formulation likely due to the granule encapsulating technology used for the oral powder formulation and is not expected to be clinically significant. Tenofovir mean $AUC_{0\text{-}last}$ and mean AUC_{inf} were similar between the oral powder and tablet formulations. TDF was safe and well tolerated when administered to healthy subjects as either the oral powder or tablet formulation.

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/s/

DIONNA J GREEN
12/23/2011

SARAH M ROBERTSON
12/23/2011