CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022577Orig1s000

MICROBIOLOGY REVIEW(S)

Virology Review
Division of Antiviral Products

NDA #: 22-577 SDN 000 **Reviewer**: N. Battula, Ph.D.

Date submitted: June 16, 2011 Date received: June 16, 2011
Date Assigned: June 17, 2011 Date reviewed: November 19, 2011

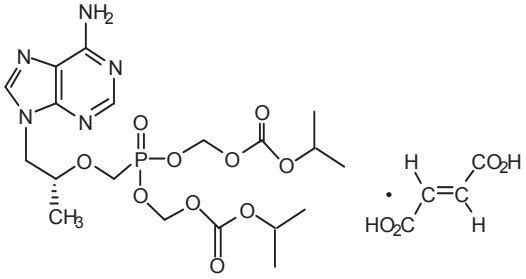
Additional submissions reviewed		Date submitted
sNDA #: 21-356 SE9-038	SDN 776	September 30, 2011
NDA #: 21-356S E9-038	SDN 521	July 18, 2011
NDA #: 22-577	SDN 009	September 30, 2011
NDA #: 22-577	SDN 012	November 4, 2011
NDA #: 22-577	SDN 013	October 13, 2011

Sponsor: Gilead Sciences.
333 Lakeside Drive
Foster City, CA 94404

Product name(s): Proprietary**:** VIREAD®
Nonproprietary**:** Tenofovir disoproxil fumarate
Chemical: 9-[(R)-[[bis [[isopropoxycarbonyl)oxy] methoxy-phosphoinoyl] methoxy]-propyl] adenine fumarate (1:1)

Mol. formula = $C_{23}H_{34}N_5O_{14}P$ Mol. weight = 635.32

Structural formula:



Dosage form: Tablets in strengths of 150, 200, 250 and 300 mg of TDF and powder 40 mg of TDF per gram of powder

Route of administration: Oral

Drug category: HIV-1 reverse transcriptase inhibitor (nucleotide analogue)

Indication: Treatment of HIV-1 infection in children 2- <12 years of age in combination with other antiretroviral agents

Related documents: IND 52, 849 and NDA 21-356

Background and Summary: With submission of this original pediatric NDA, the applicant is seeking to gain marketing approval for Viread® (tenofovir disoproxil fumarate) oral powder for the treatment of HIV-1 infection in combination with other antiretroviral agents for pediatric subjects 2 to <12 years of age. The applicant is also seeking an expansion to the current indication for the use of Viread® in combination with other antiretroviral agents for the treatment of pediatric subjects 2 to <12 years of age. In support of this approval, the applicant submitted a pivotal clinical efficacy, safety and pharmacokinetics study GS-US-104-0352, a phase 3 randomized, open-label comparator-controlled study in virologically suppressed pediatric subjects of 2 to <12 years of age who were receiving highly active antiretroviral therapy (HAART) regimen containing stavudine or zidovudine at study entry.

Tenofovir disoproxil fumarate (TDF; Viread®) 300 mg tablet was approved on October 31, 2001 for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents. This approval stipulated that the sponsor perform pediatric studies as a post marketing commitment for Viread® and also to fulfill the terms of the pediatric written request under the Pediatric Research Equity Act[1] to conduct studies in HIV-1 infected pediatric patients. The sponsor has been developing pediatric formulations and conducting studies in pediatric patients with HIV-1 infection.

The submission also includes an efficacy supplement to NDA 21-356 SE9-038 which introduces 3 reduced strength tablets containing 150 mg, 200 mg and 250 mg tenofovir disoproxil fumarate for subjects weighing 17 to <35 kg. The formulation for the lower strength tablets is identical to the currently approved 300 mg tablet with the exception of the color of the film-coat. The specification tests and the acceptance limits for the Viread® tablets, 150 mg, 200 mg and 250 mg are the same as those applied to the approved Viread® 300 mg tablet. For details of the lower strength formulations see the Product Quality review by Kambhapati Rao, Ph.D., and the biopharmaceutics review by Selen Arzu, Ph.D.

As a result of conducting the pediatric studies and the study reports submitted, on March 24, 2010 the FDA approved Viread® in combination with other antiretroviral agents for

[1] See the list of abbreviations

the treatment of pediatric patients 12 to <18 years old. This present NDA 22-577 contains the safety, efficacy and PK data of a Phase 3 clinical study report for the study GS-US-104-0352 in which younger children 2 to <12 years of age were treated using a new powder formulation of TDF at 8 mg/kg up to 300 mg/day.

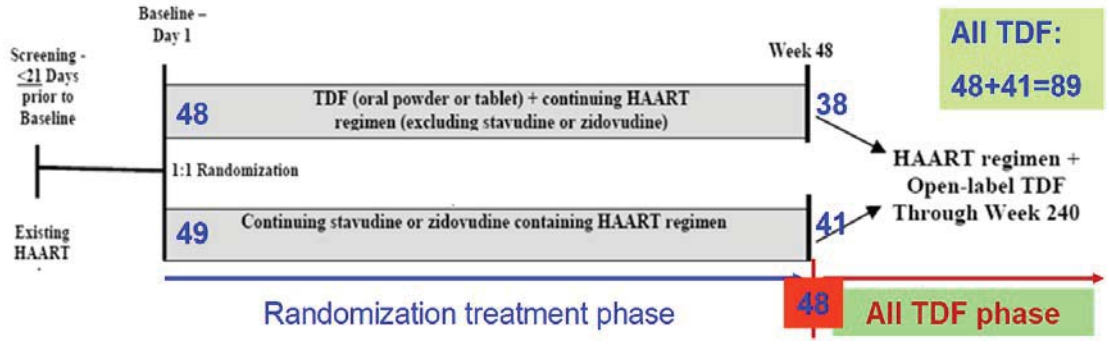
Study GS-US-104-0352 compared the relative effect of substituting Viread® to stavudine or zidovudine containing HAART regimen in 2 to <12 year old virologically suppressed (≤ 400 HIV-1 RNA copies/ml) HIV-1 infected children. This review pertains to the clinical virology aspects of the submission. For additional details regarding safety, pharmacokinetics and efficacy see the clinical review by Vargas-Kasambira Tafadzwa, M.D., clinical pharmacology review by Dionna Green, M.D., and statistical review by Zeng Wen, Ph.D.

GS-US-104-0352 Study 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."

This is a 240 week ongoing multicenter study being conducted at 9 study sites: 6 sites in the US (n=22), one site in Panama (n=72) and 2 sites in the United Kingdom (n=3). The study is being conducted in two phases an initial randomized comparator controlled phase for 48 weeks followed by an extended non-controlled phase for two consecutive study periods of 96 weeks each.

The study design for GS-US-104-0352 and the disposition of the subjects are presented in Figures 1 and 2, respectively.

Figure 1. Study Schema for GS-US-104-0352



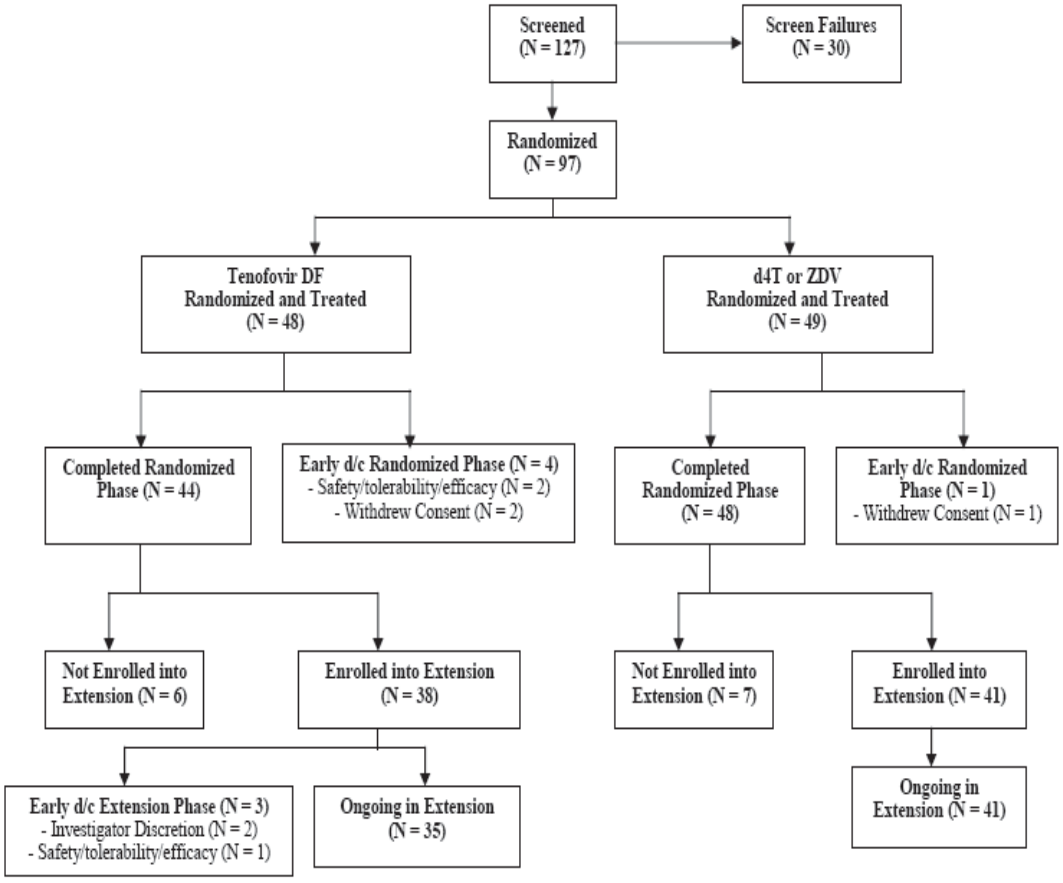
Source: Modified from the Week 48 Interim Clinical Study Report, page 33

Weeks 0-48: In the initial 48 weeks of the study the enrollees were randomized in a 1:1 ratio to either replace stavudine or zidovudine with tenofovir DF (Treatment Group A) or continue stavudine or zidovudine (Treatment Group B) in their current HAART regimen. Randomization was stratified by whether a subject was currently on stavudine or zidovudine. Changes to the subject's pre-study HAART regimen were only permitted for toxicity management. Otherwise, each HAART regimen was to remain as prescribed prior to the study entry. Efficacy and safety measurements were done at each clinical visit at weeks 2, 4, 8, 16, 24, 36 and 48.

After completing 48 weeks of treatment in their assigned treatment groups, eligible subjects from both treatment groups were given the option to roll over into 2 consecutive 96-week study extensions to receive open-label tenofovir DF for a total duration of up to 240 weeks. Subjects initially randomized to stavudine or zidovudine could switch treatment to tenofovir DF in the study extension if the investigator determined that tenofovir DF would be safe and beneficial for the subject.

Weeks 48-144: 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 tenofovir DF in a 96-week study extension period. Subjects initially randomized to treatment group B were switched from stavudine or zidovudine to tenofovir DF in the study extension if the investigator determined that tenofovir DF would be safe and beneficial for the subject. Efficacy and safety measurements were performed every 12 weeks in the extension phase.

Figure 2. Disposition of the pediatric subjects in study GS-US-104-0352



Source: From the Week 48 Interim Clinical Study Report, page 77

Figure 2 shows that of the 127 screened subjects, 97 were randomized at 9 sites; six sites in the United States (n = 22), two sites in the United Kingdom (n = 3), and one site in Panama (n = 72). Forty-eight subjects were randomized to the tenofovir DF group and 49 subjects were randomized to the stavudine or zidovudine group. All 97 randomized subjects were treated with study medication and comprised the RAT and ITT analysis sets. Out of the 97 randomized and treated subjects, 92 completed the 48-week randomized phase (44 subjects [91.7%] in the tenofovir DF group and 48 subjects [98.0%] in the stavudine or zidovudine group).

Extension Phase: In the tenofovir DF group, 38 of the 44 subjects who completed the randomized phase continued on to the extension phase of the study. Six subjects did not consent to continue into the extension phase. In the stavudine or zidovudine group, 41 of the 48 subjects who completed the randomized phase continued on to the extension phase

of the study. Six subjects did not consent to continue into the extension phase. One additional subject did not continue in the extension phase due to investigator discretion. Seventy-nine subjects received tenofovir DF in the extension phase (38 who were initially randomized to tenofovir DF and 41 who were initially randomized to stavudine or zidovudine). At the time of the data cut off for this analysis, 76 subjects are ongoing in the extension phase and 3 have discontinued from the extension phase.

The primary objective of the study was to assess the efficacy of switching to tenofovir DF compared to continuing on stavudine or zidovudine in maintaining virologic suppression (plasma HIV-1 RNA < 400 copies/mL) in HIV-1 infected children at Week 48

The secondary objectives of the study (Weeks 0–48) were:

- 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

A secondary objective to be evaluated beyond Week 48 (Weeks 0–240) is:

- To evaluate the long-term efficacy, safety, and tolerability of treatment with tenofovir DF through up to 240 weeks of drug exposure.

Study Population: The study enrolled HIV-1 infected male and female subjects, 2 to < 12 years of age, with plasma HIV-1 RNA < 400 copies/mL. Subjects were naive to tenofovir DF, and were on a stable stavudine or zidovudine-containing HAART regimen for at least 12 weeks prior to study entry. [(Subjects enrolled in another Gilead-sponsored Study GS-US-162-0111 were eligible for inclusion in this study, since they were receiving stavudine or zidovudine, and were virologically suppressed (HIV-1 RNA < 400 copies/mL), with no significant safety concerns. For these subjects, the age requirement for study entry was 2 to < 16 years of age. Five subjects from study, GS-US-162-0111, who were up to 16 years of age were enrolled into this study.)]

Subjects receiving cancer chemotherapeutic agents, systemic corticosteroids, IL-2 or other immunomodulating agents or investigational agents were excluded from the study.

Measurements: HIV-1 RNA in plasma samples was analyzed using the Roche COBAS® Amplicor HIV-1 Monitor Test Version 1.5. HIV-1 genotyping was conducted using the GeneSeq™ Assay (Monogram Biosciences, Inc.). By GeneSeq™ genotyping method

HIV-1 RT amino acids 1-305 and PR amino acids 1–99 are sequenced. $CD4^+$ T-cell counts and $CD4^+$ T-cell percentage were assessed using a dual-platform method, in which lymphocyte counts were assessed by an automated hematology analyzer and CD4% was obtained by flow cytometry.

Virology-related baseline characteristics: Table 1 shows some of the baseline characteristics of the randomized and treated subjects. Overall the baseline characteristics were similar among the treatment groups.

Table 1. Study GS-US-104-0352: virology related baseline characteristics[1]

Characteristics[2]	TDF (N = 48)	d4T or ZDV (N = 49)	(d4T or ZDV)/[3] TDF (N = 41)	All TDF[3] (N = 89)
Male (%)	23 (56.1%)	21 (43.8%)	29 (59.2%)	44 (49.4%)
Female (%)	27 (56.3%)	20 (40.8%)	18 (43.9%)	45 (50.6%)
Age years	7	7	8	8
Mean (SD)	7 (3.3)	7 (2.6)	8 (2.6)	8 (3.0)
Min, Max	2, 15	2, 14	3, 15	2, 15
HIV-1 RNA, n/N				
< 400 copies/mL	47/48	47/49	38/41	85/89
< 50 copies/mL	36/48	41/49	34/41	70/89
$CD4^+$ Cell Count (cells/mm^3)				
Mean (SD)	1190 (541.7)	1144 (388.4)	1167 (359.3)	1179 (464.2)
Min, Max	500, 3671	407, 2313	387, 2048	387, 3671
CD4%				
Mean (SD)	33.9 (7.44)	33.0 (6.82)	33.2 (5.75)	33.6 (6.69)
Min, Max	18.0, 48.0	17.0, 51.0	22.0, 43.0	18.0, 48.0

[1] Source: consolidated from the applicant's summary of clinical efficacy, Table 4 pages 26-27

[2] Denominator is the number of randomized and treated subjects within the treatment group.
[3] Baseline values for the (d4T or ZDV)/TDF and all TDF groups (excluding sex, ethnicity, and race) reflect the last non-missing value collected prior to the first dose of tenofovir DF.

Antiviral activity (primary efficacy endpoint; subjects with plasma HIV-1 RNA < 400 copies/ml): the antiviral activity data in Table 2 shows that at Week 48, 83.3% of subjects (40/48) in the tenofovir DF group and 91.8% of subjects (45/49) in the stavudine or zidovudine group had HIV-1 RNA concentrations < 400 copies/mL (M = F, ITT analysis set). An estimate of the difference in proportions and a two-sided 95% CI about the difference in proportions (tenofovir DF group minus stavudine or zidovudine group) for the primary endpoint was constructed (−8.5%; 95% CI [−21.5% to 4.5%]). Since the lower confidence bound of the difference between treatment groups was −21.5%,

tenofovir DF did not meet the criteria (lower confidence bound of the difference between treatment groups greater than −15%) for treatment noninferiority.

For M = E using the ITT analysis set, 90.9% of tenofovir DF subjects (40/44) and 93.8% of stavudine or zidovudine subjects (45/48) had HIV-1 RNA concentrations < 400 copies/mL at Week 48 (Table 2). The difference in the proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL was −2.8% and the 95% CI was −13.8% to 8.1%. Since the lower confidence bound of the difference in proportions between treatment groups was −13.8%, tenofovir DF met the criteria for treatment noninferiority.

Overall the result in Table 2 below indicate that numerically the comparator stavudine-zidovudine treatment group showed higher percentage of antiviral activity relative to the TDF treatment group.

Table 2. Study GS-US-104-0352: proportion of subjects with plasma HIV-1 RNA < 400 Copies/ml at Week 48 (ITT analysis set)

Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	p-value[a]	Difference (95% CI)[b, c]
Missing = Failure[d]				
At Week 48	40/48 (83.3%)	45/49 (91.8%)	0.23	–8.5% (–21.5% to 4.5%)
Missing = Excluded[e]				
At Week 48	40/44 (90.9%)	45/48 (93.8%)	0.71	–2.8% (–13.8% to 8.1%)

Source: from Week 48 Interim Clinical Study Report, Page 89

[a]p-values displayed to test for between group differences (randomized phase) are from a Fisher's Exact test.
[b]The confidence interval for the proportion estimate for a treatment group is based on the Exact method.
[c]The 95% confidence interval on the difference in proportions between randomized treatment groups is based on the normal approximation.
[d]Denominator (for %) is the number of ITT Subjects (subjects with missing HIV-1 RNA data counted as failure).
[e]Denominator (for %) is the number of ITT Subjects with non-missing HIV-RNA data at the visit

Antiviral activity (secondary efficacy endpoint; subjects with plasma HIV-1 RNA < 50 copies/ml): data in Table 3 show that at Week 48, 70.8% of subjects (34/48) in the tenofovir DF group and 85.7% of subjects (42/49) in the stavudine or zidovudine group had HIV-1 RNA concentrations < 50 copies/ml (M = F). The difference in the proportion of subjects with HIV-1 RNA concentrations < 50 copies/ml between the tenofovir DF and stavudine or zidovudine group was −14.9% and the 95% CI was −31.0% to 1.3%.

Table 3. GS-US-104-0352: Proportion of subjects with plasma HIV-1 RNA < 50 copies/ml at Week 48 (M = F; ITT analysis set)

Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 (n, %)[a,b]	TDF (N = 48)	d4T or ZDV (N = 49)	p-value[c]	Difference (95% CI)[d,e]
At Week 48	34/48 (70.8%)	42/49 (85.7%)	0.089	–14.9% (–31.0% to 1.3%)

Source: Week 48 Interim Clinical Study Report, Page 90

[a]Roche PCR Ultrasensitive assay. Data collected after 1st dose open-label tenofovir DF or last dose + 2 days (if terminated) excluded.
[b]Denominator (for %) is the number of ITT Subjects (subjects with missing HIV-1 RNA data counted as failures).
[c]p-values displayed to test for between group differences (randomized phase) are from a Fisher's Exact test.
[d]The confidence interval for the proportion estimate for a treatment group is based on the Exact method.
[e]The 95% confidence interval on the difference in proportions between randomized treatment groups is based on the normal approximation.

Antiviral activity (primary efficacy endpoint; subjects with plasma HIV-1 RNA < 400 copies/ml by snapshot analysis): Table 4 shows the primary efficacy endpoint using the snapshot analysis that was not defined in the study protocol (post-hoc analysis). At Week 48, 42/48 subjects (87.5%) in the tenofovir DF group and 43/49 subjects (87.8%) in the stavudine or zidovudine group had virologic success (ITT analysis set). The difference in the percentage of subjects with virologic success was −0.3% and the 95% CI was −13.4% to 12.9%. Since the lower bound of the CI for the difference between treatment groups was greater than −15%, tenofovir DF met the criteria for treatment noninferiority using this analysis.

Table 4. GS-US-104-0352: Snapshot analysis of subjects with HIV-1 RNA < 400 copies/ml at Week 48 (ITT analysis set)

Virologic Response at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	Difference (95% CI)[b]
Virologic Success	42 (87.5%)	43 (87.8%)	–0.3% (–13.4% to 12.9%)
Virologic Failure[c]	5 (10.4%)	5 (10.2%)	
No Virologic Data at Week 48 Window	1 (2.1%)	1 (2.0%)	
Discontinued Study Due to AE or Death[d]	0	0	
Discontinued Study for Other Reason[e]	1 (2.1%)	1 (2.0%)	
Missing Data during Window but on Study	0	0	

Source: summary of clinical efficacy page 31

[a] Data collected up to the last randomized phase dose + 2 days were included.
[b] The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.
[c] Virologic failure includes subjects with HIV-1 ≥ 400 copies/ml in the Week 48 window; subjects who discontinued for lack of efficacy and with no HIV-1 RNA data in the Week 48 window; subjects who changed antiretrovirals for reasons not permitted in the protocol; and subjects who discontinued for reasons other than AEs, death, and lack of efficacy and the last available HIV-1 RNA value before the start of the Week 48 window is ≥ 400 copies/mL.
[d] Category includes subjects who discontinued due to AE or death if this resulted in no virologic data on treatment during the Week 48 window.
[e] Category includes 1 subject from each treatment group who withdrew consent.

Antiviral activity (secondary efficacy endpoint; subjects with plasma HIV-1 RNA < 50 copies/ml by snapshot analysis): Table 5 shows a snapshot analysis of the virologic response at Week 48 for the number and percentage of subjects with HIV-1 RNA < 50 copies/ml. At Week 48, 36/48 (75.0%) of subjects in the tenofovir DF group and 39/49 subjects (79.6%) in the stavudine or zidovudine group had HIV-1 RNA < 50 copies/ml (ITT analysis set). The difference in the percentage of subjects with HIV-1 RNA < 50 copies/ml between the tenofovir DF and stavudine or zidovudine group was −4.6% and the 95% CI was −21.2% to 12.1%.

Table 5. Snapshot Analysis of Subjects with HIV-1 RNA < 50 copies/ml at Week 48 (ITT analysis)

Virologic Response at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	Difference (95% CI)[b]
Virologic Success	36 (75.0%)	39 (79.6%)	–4.6% (–21.2% to 12.1%)
Virologic Failure[c]	11 (22.9%)	9 (18.4%)	
No Virologic Data at Week 48 Window	1 (2.1%)	1 (2.0%)	
Discontinued Study Due to AE or Death[d]	0	0	
Discontinued Study for Other Reason[e]	1 (2.1%)	1 (2.0%)	
Missing Data during Window but on Study	0	0	

Source: from the Summary of clinical efficacy page 35, Table 12

[a] Data collected up to the last randomized phase dose + 2 days were included.
[b] The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.
[c] Virologic failure includes subjects with HIV-1 ≥ 50 copies/mL in the Week 48 window; subjects who discontinued for lack of efficacy and with no HIV-1 RNA data in the Week 48 window; subjects who changed antiretrovirals for reasons not permitted in the protocol; and subjects who discontinued for reasons other than AEs, death, and lack of efficacy and the last available HIV-1 RNA value before the start of the Week 48 window is ≥ 50 copies/mL.
[d] Category includes subjects who discontinued due to AE or death if this resulted in no virologic data on treatment during the Week 48 window.
[e] Category includes 1 subject from each treatment group who withdrew consent.

Changes in baseline in CD4% at week 48: Table 6 shows the summary of changes from baseline in CD4% at week 48. The data indicated that there were minimal changes in CD4% from baseline in either of the treatment groups. The median change at Week 48 was 0 in the tenofovir DF group and 1% in the stavudine or zidovudine group (M = E, ITT analysis set); the difference (95% CI) between the treatment groups was −0.8% (−2.7, 1.1)

Table 6. Change from Baseline CD4% at Week 48 (M = E; ITT Analysis)

CD4%[a]	TDF (N = 48)	d4T or ZDV (N = 49)	p-value[b]	Difference (95% CI)[c]
Baseline				
N	48	49		
Mean (SD)	33.9 (7.44)	33.0 (6.82)	0.42	1.0 (–1.9 , 3.8)
Median	34.0	33.0		
Q1, Q3	28.0, 39.5	28.0, 37.0		
Min, Max	18.0, 48.0	17.0, 51.0		
Change at Week 48				
N	46	48		
Mean (SD)	0.3 (4.49)	1.1 (4.73)	0.45	–0.8 (–2.7 , 1.1)
Median	0.0	1.0		
Q1, Q3	–3.0, 3.0	–2.0, 3.5		
Min, Max	–11.0, 11.0	–10.0, 20.0		

Source: from the Summary of clinical efficacy page 38, Table 15

[a] For the randomized treatment groups, data collected after first dose of open-label tenofovir DF were excluded.

[b] The p-value comparing between treatment group differences (randomized phase) is from a Wilcoxon rank sum test.

[c] The 95% CI on the mean difference between randomized treatment groups is based on the normal approximation.

Virology substudy- Resistance evaluation: Gilead conducted a virology genotyping substudy on all subjects who discontinued the study due to virologic failure, or who had HIV-1 viral RNA ≥ 400 copies/ml at Weeks 48, 96 and 144, or upon early discontinuation (prior to January 14, 2010, the cutoff date). The sequence of HIV-1 RT (amino acids 1-305) and PR (amino acids 1–99) were determined using the GeneSeq™ Assay (Monogram Biosciences, Inc.) Baseline genotyping was not conducted due to the low HIV-1 viral load (<400 copies/ml) at study entry.

Out of the 89 subjects who received tenofovir DF in the study, 19 subjects (21%) qualified for the virology substudy. These 19 subjects comprised the resistance analysis population. Banked plasma samples from the virologic failures were subjected for post baseline HIV-1 genotyping and data could be obtained for 17 subjects (Table 7). HIV-1 samples from two subjects could not be genotyped due to assay failure. Twelve of the 17 subjects started on TDF at randomization.

Table 7. GS-US-104-0352: Summary of HIV-1 drug resistance substitutions

Subject[a]	Treatment Group	Visit[b]	Sub-type	Major PR Mutations[c]	Major RT Mutations[d]	Concomitant ART
1578-9008	TDF	Week 144	B	D30N, L33F, I84V	M41L, D67N, M184V, L210W, T215F	3TC, LPR/r
1578-9010	TDF	Week 48	B	None	M184V	3TC, LPR/r
1578-9019	TDF	Week 48	B	L90M	M41L, M184V, L210L/W, T215C/Y	3TC, LPV/r
1578-9021	TDF	Week 144	B	None	M184V	3TC, LPV/r
1578-9022	(d4T or ZDV)/TDF	Week 96	B	None	None	3TC, LPV/r
1578-9033	TDF	Week 48	B	None	None	3TC, LPV/r
1578-9050	TDF	Week 48	B	M46M/I	M184V, P225P/H	3TC, LPV/r
		Week 96	B	None	M184V	3TC, LPV/r
		Week 144	B	None	M184V	3TC, LPV/r
1578-9052	(d4T or ZDV)/TDF	Week 96	B	None	M184V	FTC, LPV/r
1578-9056	TDF	Early Disc. (Week 95)	B	None	D67D/N, K70K/R, M184V, T215T/I, K219K/E/Q	3TC, LPV/r
1578-9057	TDF	Week 96	B	None	None	3TC, LPV/r
		Early Disc. (Week 146)	B	None	None	3TC, LPV/r
1578-9059	TDF	Week 96	B	None	M184M/V	3TC, LPV/r
		Week 144	B	None	M184M/V	3TC, LPV/r
1578-9063	TDF	Week 96	B	None	M184V	3TC, LPV/r
1800-9064	TDF	Week 60	B	None	V108I, Y181C	ABC, LPV/r
1578-9074	(d4T or ZDV)/TDF	Week 48	B	None	M41M/L, M184V	3TC, LPV/r
1578-9086	(d4T or ZDV)/TDF	Week 48	B	None	M184M/V	3TC, LPV/r
1578-9087	(d4T or ZDV)/TDF	Week 48	B	None	M184V	3TC, LPV/r
3106-9093	TDF	Week 4	A	None	K65R, Y181C	ABC, 3TC, NVP

ABC = abacavir; FTC = emtricitabine; 3TC = lamivudine; LPV/r = lopinavir boosted with ritonavir; NVP = nevirapine; d4T = stavudine; TDF = tenofovir DF; ZDV = zidovudine

[a] Genotyping assay for subject 3106-9093 failed with the week 2 sample (with 238 HIV-1 RNA copies/ml), but was successful with the 4 week sample (with 1130 HIV-1 RNA copies/ml.)

[b] Subjects in the (d4T or ZDV)/TDF group had their baseline reset after they switched to tenofovir DF at Week 48.

[c] Major protease (PR) drug resistance substitutions included in this analysis were D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, and L90M.

[d] Major reverse transcriptase (RT) substitutions associated with drug resistance included in this analysis were M41L, A62V, K65R, D67N, T69insertion, K70E/R, L74V/I, V75I, F77L, L100I, K101E/H/P, K103N, V106A/M, V108I, Y115F, F116Y, Q151M, Y181C/I/V, M184V/I, Y188L/C/H, G190S/A, L210W, T215Y/F, K219Q/E/N/R, and P225H. The T215 reversion substitutions T215A/C/D/E/G/H/I/L/N/S/V were also listed.

Data in the drug resistance Table 7 show that one subject (3106-9097) in the tenofovir DF group had two substitutions K65R and Y181C. This subject had an increase in viral load early in the study (HIV-1 RNA was < 50 copies/ml at baseline, 238 copies/ml at Week 2, and 1130 copies/ml at Week 4) and was discontinued from the study after Week 4. The 2-week discontinuation sample was sent to Monogram Biosciences for genotyping; however, no genotype was obtained due to assay failure. The Week 4 plasma was sent to GSI for HIV-1 genotyping and was successfully genotyped. The HIV-1 RT substitutions K65R and Y181C were detected in the sample of this 3 year old subject. This subject prior to switching to TDF was on a 4-drug HAART with AZT+ABC+3TC+NVP for about 8 months between July 2007 and March 2008. The resistance pattern observed in this subject is consistent with the use of tenofovir DF and the other concomitant antiretroviral drugs (ABC, 3TC, and NVP). This subject had subtype A HIV-1. The rapid detection of HIV-1 resistance substitutions, notably the K65R substitutions by Week 4, is indicative of preexisting resistance archived at study entry. However, development of these resistance substitutions after switching to TDF cannot be ruled out. No other subject analyzed in this study had HIV-1 with the tenofovir DF-associated substitution, K65R.

In the 17 virologic failure subjects analyzed, the most common NRTI resistance associated substitution was M184V (12 subjects, 71%), followed by thymidine-analog associated mutations (TAMs) (4 subjects, 24%). All subjects with TAMs also had M184V. All of the failure subjects also had past stavudine or zidovudine therapy, which could select for TAMs, and were also taking lamivudine or emtricitabine, which could select for M184V/I.

Conclusions and Recommendations: To fulfill the post approval commitment and to comply with the Pediatric Research Equity Act to carryout studies in HIV-1 infected pediatric subjects, Gilead conducted the study GS-US-104-0352 entitled, "A Phase 3, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy." This is a 240 week ongoing multicenter study being conducted at 9 study sites: 6 sites in the US, one site in Panama and 2 sites in the United Kingdom. The study is being conducted in two phases an initial phase for 48 weeks followed by an extended phase of two consecutive study periods of 96 weeks each.

Results of the study showed that virologically suppressed children on HAART regimen when switched to TDF from stavudine or zidovudine containing regimen or keeping on their stavudine or zidovudine containing HAART regimen, the subject's antiviral activity

remained suppressed and the $CD4^+$ cells or CD4% were maintained with no significant differences between the two treatment groups. Based on the results of the study the sponsor is requesting an expansion to the current indication for the use of Viread® to include the treatment of HIV-1 infection in combination with other antiretroviral agents in pediatric subjects 2- <12 years of age.

In this study one virologically failed subject out of the 17 virologically failed children showed the emergence of the K65R, a substitution associated with TDF resistance. In this study population of HAART experienced children the most common resistance associated substitution was the NRTI associated M184V followed by thymidine-analog associated substitutions. These resistance results observed in this study are similar to the patterns of resistance-associated substitutions observed among treatment-experienced, HIV-1 infected adolescents 12 to <18 years of age and treatment-experienced adults. Therefore no changes to the resistance portion of the Microbiology section of the package insert are warranted at this time.

There are no microbiology-related issues with this study in 2 to <12 years of age children and with regard to microbiology this NDA is approved.

_____

Narayana Battula, Ph.D.
Microbiologist

Concurrence:
DAVP/TLMicro: J.J. O'Rear _____ Date _____

Abbreviations

ARV	Antiretroviral therapy
CI	Confidence interval
CSR	Clinical study report
BMD	Bone mineral density
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type-1
ITT	Intent-to-treat
M = E	Missing = Excluded
mL	Milliliter(s)
NDA	New drug application
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleotide reverse transcriptase inhibitor
OBR	Optimized background regimen
PCR	Polymerase chain reaction
PR	Protease of HIV-1
PI	Protease inhibitor
PK	Pharmacokinetic
PR	Protease
PREA	Pediatric Research Equity Act
RAT	Randomized and treated
RT	Reverse transcriptase
RNA	Ribonucleic acid
TAM	Thymidine analog-associated mutation
TDF	Tenofovir DF, Viread®
µg	Microgram
µL	Microliter

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

/s/

NARAYANA BATTULA
12/09/2011

JULIAN J O'REAR
12/09/2011

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 22577 **Applicant:** Gilead **Stamp Date:** June 16, 2011

Drug Name: VIREAD (TDF) **NDA Type:**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
4	On its face, has the applicant submitted cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			N/A (no virology summary or study reports provided: necessity of these is a review issue)
7	Has the applicant submitted the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		(b) (4) conducted the resistance analyses and viral load was measured with Roche assays.
9	Has the applicant submitted draft labeling consistent with			No revisions to label section 12.4

File name: 5_Microbiology Filing Checklist for a NDA or Supplement 010908

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	current regulation, divisional and Center policy, and the design of the development package?			Microbiology
10	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?			No revisions to to label section 12.4 Microbiology proposed
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?			N/A
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			N/A

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

(b) (4)

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no virology specific review issues at this time.

(Nara Battula, Ph.D.)
Reviewing Microbiologist Date

Jules O'Rear, Ph.D. July 11, 2011
Microbiology Team Leader Date

File name: 5_Microbiology Filing Checklist for a NDA or Supplement 010908

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

/s/

JULIAN J O'REAR
07/11/2011