NDA 21-356 / SN

Rat Carcinogenicity Study

CONFIDENTIAL FINAL

RESEARCH REPORT

AN ORAL CARCINOGENICITY STUDY OF TENOFOVIR DISOPROXIL FUMARATE (TENOFOVIR DF) IN THE ALBINO RAT VOLUME I

For: Gilead Sciences
353 Lakeside Drive
Foster City
California 94404
U.S.A

Project No.:

Gilead Study No. R990204

Date:

PROJECT NO.

ABSTRACT

The purpose of this study was to investigate the potential carcinogenicity and chronic toxicity of Tenofovir Disoproxil Fumarate (Tenofovir DF) during daily oral administration to the Sprague-Dawley rat for 103/104 consecutive weeks. Tenofovir DF was administered to rats (60/sex/group for main study) at dose levels of 0, 10/300, 30 and 100 mg/kg/day. Following a review of the available data by the FDA, the lowest dose level of 10 mg/kg/day was increased to 300 mg/kg/day on Day 10. To obtain a toxicokinetic (TK) profile at 300 mg/kg/day, an additional group of 16 males and 16 females was added to the study and was dosed for a period of 13 weeks. Further toxicokinetic profiling was later required and an additional 24 males and 24 females were added to Groups 1 to 4; these animals were dosed for a period of 26 weeks at dose levels of 0, 30, 100 or 300 mg/kg/day. The final design of the study is summarized in the table below.

Group No. Identification	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Numbers of Animals: Main Study Males	Main Study Females	TK Groups Males	TK Groups Females
1 Vehicle Control	0	10	60	60	16[1]+24[3]	16[1]+24[3]
2 Tenofovir DF	10/300*	10	60	60	16+24	16+24
3 Tenofovir DF	30	10	60	60	16+24	16+24
4 Tenofovir DF	100	10	60	60	16+24	16+24
5 Health Screen	-	-	10	10	-	-
6 Tenofovir DF	300	10	-	-	16[2]	16[2]

* Following consultation with the FDA the dose for Group 2 was increased to 300 mg/kg/day on Day 10.
1 Initial TK group (Set 1)
2 An additional group of TK animals were added to the study (Group 6, Set 2, to obtain plasma data from Day 1, 30, 60 and 90 at the revised dose level of 300 mg/kg/day).
3 Additional populations of animals of 24 males and 24 females were added to Groups 1 to 4 to evaluate TK response for a period of 26 weeks (Set 3)

The following parameters were measured during the study: Mortality, signs of ill health and reaction to treatment (twice daily), detailed physical examination (weekly), body weights (weekly and prior to necropsy), food consumption (weekly), and ophthalmology (once pretreatment, during Week 52, and again during Week 103, females Group 3 and Week 104). Red and white blood cell counts were determined and blood smears were obtained from all animals at Weeks 52, 78 and 103/104. Toxicokinetic sampling was performed on Day 1 and Day 30 for Groups 1 to 4 original population (Set 1); Day 1, 30, 60 and 90 for Group 6 (Set 2); and Day 1 and 180 for Groups 1 to 4, additional population (Set 3). On each occasion samples were obtained at pre-dose, 15 minutes, 30 minutes, 1, 2, 4, 8, and 24 hours post dose for 2-3 animals/sex/group/time point. Due to closure of the Sponsors designated laboratory only data from Set 3 (Groups 1 to 4) have been reported. Gross pathology (necropsy) was performed on all animals, including the TK and health screen animals. Histopathology was performed on all main study animals from all groups.

The results may be summarized as follows:

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Treatment related clinical signs were restricted to salivation. Salivation following dose administration was noted for all animals receiving 100 or 300 mg/kg/day, with a higher incidence being seen in animals receiving 300 mg/kg/day.

A treatment related reduction in group mean body weight of 4-5% was recorded at Week 24, this effect on body weight was seen during Weeks 24 to 80 for animals receiving 100 or 300 mg/kg/day when compared to the controls, the differences for the male animals on occasion attaining statistical significance. From Week 80, onwards, group mean body weights for treated animals were generally comparable to the controls.

There were no treatment-related effects on food consumption, hematology parameters or ophthalmoscopy.

Following the first oral dose in male rats, the calculated mean AUC_{inf} values were 2.53, 5.82 and 19.36 µg.h/mL at the 30, 100 and 300 mg/kg/day dose levels, respectively. For female rats, the corresponding calculated mean AUC_{inf} values were 2.39, 5.27and 14.18 µg.h/mL, respectively. On Day 180, mean plasma $AUCss_{0-24}$ values (µg.h/mL) at the 30, 100 and 300 mg/kg/day dose levels were 2.70, 6.60 and 16.69, respectively for males and 3.06, 7.46 and 15.72, respectively for females. The extent of exposure (AUC_{0-24}) of tenofovir appeared to be similar between males and females on Day 1 and 180. Cmax values were generally comparable between the sexes. Exposure was linear within each dose level but did not increase in a dose proportional fashion when doses were increased from 30 to 300 mg/kg/day.

The results of the histopathological examination revealed treatment-related lesions in the kidney. tubular karyomegaly was evident in male rats from all dosage groups with the incidence being dosage related, and in high dose females . Once daily oral administration of Tenofovir DF to rats for 103/104 consecutive weeks did not result in any increase in the incidence of neoplastic lesions in various organ and tissue systems examined. The benign and malignant neoplasms observed followed no pattern, appeared to be spontaneous in nature, and were within the limits reported for aging CD Sprague-Dawley rats.

At the request of the study Sponsor a histopathology peer review was conducted and the findings were in agreement with those of the study pathologist.

In conclusion, lifetime daily administration of Tenofovir DF at dosage levels of up to 300 mg/kg/day did not reveal any evidence of carcinogenicity in Sprague-Dawley rats.

PROJECT NO.

TABULATED SUMMARY

Group	Tenofovir DF Dose (mg/kg/day)	No./sex Main study+@	Major findings
1	0	60	None
2	10/300*	60	Decreased group mean body weight during the first three quarters of the study (up to Week 80). Renal tubular karyomegaly (28 males,16 females) Day 180 AUCss 0-24 (µg.h/mL) male, 16.69 AUCss 0-24 (µg.h/mL) female, 15.72
3	30	60	Renal tubular karyomegaly (1 male, 0 females) Day 180 AUCss 0-24 (µg.h/mL) male, 2.70 AUCss 0-24 (µg.h/mL) female, 3.06
4	100	60	Decreased group mean body weight during the first three quarters of the study (males). Renal tubular karyomegaly (6 males, 0 females) Day 180 AUCss 0-24 (µg.h/mL) male, 6.60 AUCss 0-24 (µg.h/mL) female, 7.46

+ The test article or control vehicle was dosed via oral gavage once daily for 103 (Group 3 females) or 104 weeks (all remaining Groups).
@ Due to the survival being 25% Group 3 females were euthanised during Week 103
* 10 mg/kg/day dose increased to 300 mg/kg/day on Day 10.

NDA 21-356 / SN

Mouse Carcinogenicity Study

CONFIDENTIAL

FINAL

RESEARCH REPORT

AN ORAL CARCINOGENICITY STUDY OF TENOFOVIR DISOPROXIL FUMARATE (TENOFOVIR DF) IN THE ALBINO MOUSE

VOLUME 1

For: Gilead Sciences
353 Lakeside Drive
Foster City
California 94404
U.S.A

Project No.:
Gilead Study No. M990205

Date:

ABSTRACT

The purpose of this study was to investigate the carcinogenic potential and chronic toxicity of Tenofovir Disoproxil Fumarate (Tenofovir DF) during daily oral administration to the mouse for a minimum of 104 consecutive weeks. Tenofovir Disoproxil Fumarate (Tenofovir DF) was administered to mice (60/sex/group for main study and 60 sex/group for toxicokinetic animals) at dose levels of 0, 100, 300, and 600 mg/kg/day. The design of the study is summarized in the table below.

Group No. Identification	Dose Level (mg/kg/day) Females	Dose Volume (mL/kg/day)	Numbers of Animals Main Study Males	Main Study Females	TK Group	TK Group Males
1 Vehicle Control	0	10	60	60	-	-
2 Tenofovir DF	100	10	60	60	-	-
3 Tenofovir DF	300	10	60	60	-	-
4 Tenofovir DF	600	10	60	60	60	60
5 Health Screen	-	-	10	10	-	-

The following parameters were measured during the study: Mortality, signs of ill health and reaction to treatment (twice daily), detailed physical examination (weekly), the presence of palpable masses (from Week 26 onwards), body weights (weekly), food consumption (weekly), ophthalmology (once pretreatment, Week 52, and Week 104), hematology (prior to commencement of treatment on health screen animals). Blood smears were obtained from all animals at 12, 18, and 24 months (only the control and high level smears were evaluated). Toxicokinetic sampling was performed on Day 1 and Day 180 at pre-dose, 5 minutes (Day one only), 15 minutes, 30 minutes, 1, 2, 4, 8, 12 and 24 hours post dose on 3 animals/sex/group/timepoint (high dose group only). Gross pathology (necropsy) was performed on all main group and toxicokinetic animals. Histological examination was performed on all tissues from main animals and the results were peer reviewed.

The results may be summarized as follows:

The survival rate for males and females receiving 600 mg/kg/day appeared to be decreased (but not statistically significant) when compared to the controls. For the remaining groups/sexes, the mortality rate observed appeared to be comparable to the controls. Survival was considered acceptable for mice of this strain and age.

Treatment related clinical signs were restricted to salivation. Salivation following dose administration was noted for the majority of animals receiving 300 or 600 mg/kg/day, with a higher incidence being seen in animals receiving 600 mg/kg/day.

A reduced group mean body weight was recorded for animals receiving 300 (4.2%, 0.6% for males and females respectively) or 600 (4.6%, 3.3% for males and females respectively) mg/kg/day when compared to the concurrent controls over the 104-week treatment period. The differences from the controls were dosage related and on occasion attained statistical significance. There were no effects on body weight in animals receiving 100 mg/kg/day.

There were no treatment-related effects on food consumption, hematology parameters or ophthalmoscopy.

Treatment related macroscopic changes were recorded in the intestinal tract (Intestinal dilatation) and the liver (surface irregularity) were recorded with a higher incidence being seen for animals receiving 600 mg/kg/day.

Treatment related effects were observed in the bone marrow, duodenum, kidneys, liver and testes.

The results of the histopathological examination revealed a low incidence of treatment-related lesions in the duodenum (adenoma/adenocarcinoma) at 600 mg/kg/day. Non neoplastic lesions were observed in duodenum (epithelial hyperplasia) at 100, 300 and 600 mg/kg/day; in liver (eosinophilic and basophilic cell foci, hepatocellular hypertrophy , nuclear inclusions, cyto/karyomegaly, single cell necrosis, proliferation of sinusoidal cells) and testes (vascular mineralization) at 300 or 600 mg/kg/day; and in kidneys (karyomegaly) and bone marrow (hypercellularity: myeloid) at 600 mg/kg/day. A no effect level for non- neoplastic lesions (by histological criteria) was not established in this study.

Following the first oral dose in male and female mice, concentrations of Tenofovir reached mean peak values of 11.5 and 17.6 µg/mL, respectively. The corresponding calculated mean AUCinf values (µg•h/mL) in male and female mice were 50.4 and 48.7, respectively. The extent of exposure (AUC_{0-24}) of tenofovir, appeared to be similar between the male and female mice on Day 1 , and Day 180. AUCinf on Day 1 appeared to be comparable to AUCss0-24 on Day 180 in both the male and female mice, suggesting tenofovir possesses linear toxicokinetic properties at a dose of 600 mg/kg/day.

In conclusion, lifetime daily administration of Tenofovir DF at dosage levels of up to 300 mg/kg/day given for 104 weeks did not reveal any evidence of carcinogenicity in Swiss Crl:CD^R-1(ICR)BR mice. At 600 mg/kg/day a low incidence of duodenal tumours, possibly treatment related, were observed.

TABULATED SUMMARY

Group	Tenofovir DF Dose (mg/kg/day)	No./sex Main study+	Major findings
1	0	60	None
2	100	60	Duodenum : epithelial hyperplasia Liver : hepatocellular hypertrophy (males)
3	300	60	Decreased group mean body weight Duodenum : epithelial hyperplasia Liver: eosinophilic and basophilic cell foci, hepatocellular hypertrophy, nuclear inclusions,cyto/karyomegaly and proliferation of sinusoidal cells Testes: vascular mineralisation
4	600	60	Decreased group mean body weight Duodenum : adenoma (n=1)/ adenocarcinoma (n=2) Duodenum: epithelial hyperplasia Liver: eosinophilic and basophilic cell foci, hepatocellular hypertrophy, nuclear inclusions, cyto/karyomegaly, single cell necrosis and proliferation of sinusoidal cells Kidneys: karyomegaly Bone marrow: hypercellularity: myeloid Testes: vascular mineralization <u>Day 1</u> AUC_{0-24} Males 30.9 (µg•h/mL) AUC_{0-24} Females 35.1 (µg•h/mL) <u>Day 180</u> AUC_{0-24} Males 44.3 (µg•h/mL) AUC_{0-24} Females 50.9 (µg•h/mL)

+ The test article or control vehicle was dosed via oral gavage once daily for 104 weeks.

FDA　　提出資料

(Clinical)

NDA21-356 / SN

GS-98-902

GILEAD
SCIENCES

CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Antiviral Activity of the Addition of PMPA Prodrug (Tenofovir DF) to Combination Antiretroviral Regimens in Treatment-Experienced HIV-Infected Patients
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
Study No.:	GS-98-902
Study Start Date:	
Blinded Phase	(First Patient Randomized)
Open-Label Phase	(First Patient Enrolled)
Study End Date:	
Blinded Phase	
Open-Label Phase	
Gilead Medical Signatory:	Phone: Facsimile:
Report Date:	

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was performed in compliance with the guidelines of Good Clinical Practice (GCP) and all essential documents are being archived.

3. STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Name of Sponsor: Gilead Sciences, Inc. **Name of Finished Product:** Viread **Name of Active Ingredient:** Tenofovir DF	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	***(For National Authority Use Only)***

Title of Study:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Antiviral Activity of the Addition of PMPA Prodrug (Tenofovir DF) to Combination Antiretroviral Regimens in Treatment-Experienced HIV-Infected Patients
Investigators:	(Principal Investigator); (For affiliations and addresses of the investigators, see Appendix 16.1.4.)
Study Centers:	The 24 study centers are listed in Appendix 16.1.4.

STUDY SYNOPSIS (Continued)

Publications

Schooley R, Myers R, Ruane P, et al. A Double-Blind, Placebo-Controlled Study of Tenofovir Disoproxil Fumarate (TDF) for the Treatment of HIV Infection [abstract]. Presented at 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). San Francisco, CA, September 26, 1999.

McGowan I, Myers R, Ruane P, et al. A Double-Blind, Placebo-Controlled Study of Tenofovir Disoproxil Fumarate (TDF) for the Treatment of HIV Infection [abstract]. Presented at 7th European Conference on Clinical Aspects and Treatment of HIV-Infection. Lisbon, Portugal, October 23-27, 1999.

Miller M, Margot N, Robison M, Schooley R, Mills R, McGowan I. HIV-1 RT Mutations in Patients after 24 Weeks of Tenofovir Disoproxil Fumarate (formerly PMPA Prodrug) Therapy Added to Stable Background ART [abstract]. Presented at 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, January 30-February 2, 2000.

Schooley R, Myers R, Ruane P, et al. Tenofovir Disoproxil Fumarate (TDF) for the Treatment of Antiretroviral Experienced Patients. A Double-Blind, Placebo-Controlled Study [abstract]. Presented at 40th ICAAC. Toronto, Ontario, Canada, September 18, 2000.

Miller M, Margot N, Schooley R, Mills R, McGowan I. Anti-HIV Responses and Development of RT Mutations in Antiretroviral-Experienced Patients Adding Tenofovir DF Therapy: 48 Week Genotypic Analysis of Study 902 [abstract]. 5th International Congress on Drug Therapy in HIV Infection. Glasgow, United Kingdom, October 22-26, 2000.

Schooley R, Ruane P, Myers R, et al. Tenofovir Disoproxil Fumarate (TDF) for the Treatment of Antiretroviral Experienced Patients: a 48 Week Analysis of a Randomized, Double Blind, Placebo-Controlled Study [abstract]. Presented at 5th International Congress on Drug Therapy in HIV Infection. Glasgow, United Kingdom, October 22-26, 2000.

STUDY SYNOPSIS (Continued)

Publications (continued):	Miller MD, Margot NA, Schooley R, McGowan I. Baseline and Week 48 Final Phenotypic Analysis of HIV-1 from Patients Adding Tenofovir Disoproxil Fumarate (TDF) Therapy to Background ART. Presented at 8th Conference on Retroviruses and Opportunistic Infections. Chicago, Ill, February 4-8, 2001. Naeger LK, Margot NA, Schooley R, McGowan I, Miller MD. Anti-HIV Responses and Resistance Analyses of Antiretroviral-Experienced Patients Adding Tenofovir DF Therapy: Final Baseline and Week 48 Genotypic and Phenotypic Analyses of Study 902. Presented at 3rd European Symposium on the Clinical Implications of HIV Drug Resistance. Frankfurt, Germany, February 23-25, 2001. Miller M, Johnson A, Isaacson E, Margot N. Genotypic Analyses and HIV RNA Responses in Patients after 96 Weeks of Tenofovir DF (TDF) Therapy [abstract]. 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina. July 8-11, 2001. Skowron G, Nadler J, Thompson M, et al. Tenofovir DF: An Analysis of the Open-Label Extension Phase from a Randomized, Double-Blind, Placebo-Controlled Study in Antiretroviral-Experienced Patients [abstract]. Presented at 8th European Conference on Clinical Aspects and Treatment of HIV Infection. Athens, Greece. October 28-31, 2001. Schooley R, Ruane P, Myers R, et al. Tenofovir DF: An Interim Analysis of the Open-Label Extension Phase from a 48-Week, Randomized, Double-Blind, Placebo-Controlled Study in Antiretroviral-Experienced Patients [abstract]. Presented at 41st ICAAC. Chicago, Illinois, December 16-19, 2001.
Study Period:	(First patient randomized, blinded phase) (First patient enrolled in the open-label phase) (Last patient completed 48 weeks of dosing) (Last patient observation for 48-week blinded phase) (Last patient observation for open-label phase)

STUDY SYNOPSIS (Continued)

Objectives:

The objectives of this study were:

- To evaluate the safety and tolerability of three doses of tenofovir DF when administered in combination with other antiretroviral agents for up to 48 weeks to treatment-experienced, HIV-infected patients.
- To evaluate the anti-HIV activity of three doses of tenofovir DF, as demonstrated by the magnitude and durability of decreases in HIV RNA levels and increases in CD4 cell counts when administered in combination with other antiretroviral agents for up to 48 weeks to treatment-experienced HIV-infected patients.
- To assess the effect of mutations in HIV reverse transcriptase or protease genes on virologic response to tenofovir DF.
- To evaluate the long term safety and efficacy of tenofovir DF 300 mg open label in an extended dosing phase.

Methodology:

This study consisted of two phases: a blinded phase and an open-label phase. The blinded phase was a randomized, double-blind, placebo-controlled study of the safety and efficacy of three doses of tenofovir DF (75 mg, 150 mg, 300 mg) administered in combination with other antiretroviral agents for up to 48 weeks to treatment-experienced, HIV-infected patients.

After completing 48 weeks of study visits in the blinded phase, patients were given the opportunity to continue in the open-label phase to receive tenofovir DF. The open-label phase was a non-randomized, single-arm study of the long-term safety and efficacy of open-label tenofovir DF 300 mg administered in combination with other antiretroviral agents to treatment-experienced, HIV-infected patients.

STUDY SYNOPSIS (Continued)

Number of Patients (Planned and Analyzed):	175 patients were planned for 2:2:2:1 randomization to one of four treatment groups. In addition to continuing their background antiretroviral regimen, patients received tenofovir DF at the following doses: Group 1: Tenofovir DF 75 mg once daily (N = 50) Group 2 Tenofovir DF 150 mg once daily (N = 50) Group 3: Tenofovir DF 300 mg once daily (N = 50) Group 4: Placebo (N = 25) A total of 189 patients were enrolled in the 48-week blinded phase; 54, 51, 56, and 28 patients were enrolled into groups 1, 2, 3, and 4, respectively. Of these, 135 (71%) patients continued in the open-label phase. Patients were stratified by site on the basis of three parameters: HIV-1 RNA level (< or ≥ 20,000 copies/mL), CD4 cell count (< or ≥ 200 cells/mm^3), and number of antiretroviral drugs used prior to study entry (< or ≥ 4). Twenty-four weeks after randomization, patients in group 4 (placebo) were crossed over in a blinded fashion to tenofovir DF 300 mg once daily for the remainder of the 48-week study. Patients randomized to tenofovir DF regimens were maintained on their initial blinded dose.
Diagnosis and Main Criteria for Inclusion:	HIV-infected patients who had received a stable antiretroviral regimen of not more than four antiretroviral agents for the eight weeks prior to enrollment and who had a plasma HIV-1 RNA level ≥ 400 copies/mL and ≤ 100,000 copies/mL within 15 calendar days prior to randomization.

STUDY SYNOPSIS (Continued)

Methodology: (Continued)	
Duration of Treatment:	The duration of double-blind treatment was 48 weeks. After completing 48 weeks, patients were given the option to receive open-label tenofovir DF 300 mg once daily, while being monitored for safety and efficacy, until the drug was licensed in the United States or until trials for this compound were discontinued by the Sponsor. The median duration of exposure to tenofovir DF for the 75/300 mg tenofovir DF, 150/300 mg tenofovir DF, 300/300 mg tenofovir DF and placebo crossover to 300 mg groups was 96, 100, 99, and 80 weeks, respectively.
Test Product, Dose, Mode of Administration, and Batch No.:	48-week blinded phase: 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy] methoxy]phosphinyl]methoxy] propyl]adenine fumarate 1:1 (PMPA Prodrug, tenofovir disoproxil fumarate, tenofovir DF) for oral administration at a once daily dose of 75 mg, 150 mg, or 300 mg (i.e., 1 x, 2 x, or 4 x multiples of 75-mg tablets, Lot Nos. J705, J802, and J802A, paired with matching placebo tablets in dose-appropriate fashion to maintain blind). Randomly assigned active study drug was administered for 48 weeks. Open-label phase: 9-[(R)-2[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl] methoxy]propyl]adenine fumarate 1:1 (PMPA Prodrug, tenofovir disoproxil fumarate, tenofovir DF) for oral administration at a once daily dose of 300 mg (Lot Nos. and), with lot number (150 mg) used for patients requiring dose reductions.

STUDY SYNOPSIS (Continued)

Reference Therapy, Dose, Mode of Administration, and Batch No.:	48-week blinded phase: Matching placebo for oral administration (Lot Nos. and). Patients randomly assigned to the placebo control group received matching placebo for 24 weeks, after which they crossed over to tenofovir DF 300 mg (blind maintained) for the remaining 24 weeks of the 48-week treatment period. (For patients in the original randomized active study drug groups, tenofovir DF was paired with matching placebo in dose-appropriate fashion to maintain blind.) Open-label phase: Not applicable.
Criteria for Evaluation:	
Safety:	The primary safety end point was the proportion of patients who developed ≥ grade 3 toxicity (clinical and/or laboratory). Adverse event reports, physical examinations, and laboratory tests were used to monitor patient safety. Interim safety analyses were conducted every three to six months after initiation of enrollment.
Efficacy:	The co-primary efficacy end points were the time-weighted changes from baseline average in $\log_{10}$ HIV-1 RNA levels at week 4 ($DAVG_4$) and week 24 ($DAVG_{24}$).
Statistical Methods:	
Safety:	The incidence of patients who developed ≥ grade 3 toxicity (clinical and/or laboratory) was summarized.
Efficacy:	The time-weighted change from baseline average in $\log_{10}$ HIV-1 RNA levels was calculated for week 4 post-randomization ($DAVG_4$) and week 24 post-randomization ($DAVG_{24}$) and compared among treatment groups.

STUDY SYNOPSIS (Continued)

Results:

Safety:

The incidence of most adverse events and laboratory abnormalities was similar among the active tenofovir DF groups and the placebo group over the first 24 weeks of the study. Furthermore, through 48 weeks, the incidence of most adverse events and laboratory abnormalities did not show a dose-response pattern among the active tenofovir DF groups.

During the first 24 weeks of the study, 25% of patients in the placebo group and 9% to 16% of patients in the tenofovir DF groups discontinued study drug. Through 48 weeks, 24% to 26% of the tenofovir DF-treated patients discontinued study drug. A total of 178 (99%) of the 179 patients who received tenofovir DF (the three groups randomized to tenofovir DF and the placebo crossover group) experienced at least one adverse event from time of first dose of study medication in the blinded phase through the open-label phase of the study.

During the first 24 weeks of the study, the most common adverse events in patients treated with tenofovir DF were headache, asthenia, pain, diarrhea, nausea, vomiting, rash, and pharyngitis. Of these, only diarrhea appeared to be slightly more common in tenofovir DF groups than in the placebo group. The incidences of grade 3 or 4 clinical events were similar in all four groups in the study.

During the first 24 weeks of the study, the most common grade 3 or 4 laboratory abnormalities were elevations of triglycerides and creatine kinase. These events occurred at similar frequencies in the tenofovir DF and placebo groups. A total of 35 serious adverse events (SAEs) occurred in 25 patients. One death, caused by suicide, was reported during the double-blind phase.

STUDY SYNOPSIS (Continued)

Results:
(Continued)

Safety:
(Continued)

During the open-label phase with a median exposure for the tenofovir DF groups of approximately 100 weeks, 25 SAEs occurred in 17 patients. Other than pneumonia, bone fracture, and pyelonephritis, no SAE occurred in more than one patient. One death (liver and kidney failure) occurred during the open-label phase.

For the groups originally randomized to tenofovir DF, the most common ≥ grade 3 adverse events were depression and asthenia. The most common ≥ grade 3 laboratory abnormalities were elevations of creatine kinase, triglycerides, and AST. No significant change in the types or severity of adverse events or laboratory abnormalities were observed in the open-label phase when compared with the 48-week blinded phase results.

In both the 48-week blinded and the open-label phases of study 902, no patient developed ≥ grade 2 elevation in serum creatinine. Grade 2 hypophosphatemia was seen during both the blinded and open-label phases of the study but no patients developed treatment emergent ≥ grade 3 hypophosphatemia. Most patients with grade 2 hypophosphatemia returned to ≤ grade 1 with continued tenofovir DF 300 mg daily administration.

All bone fractures seen in both the blinded and open-label phases of study 902 have been trauma related. Through 48 weeks, mean bone mineral density reductions were < 1.7% in all groups. In the open-label phase, there was no increase in the bone fracture rate when compared to the 48-week blinded phase.

STUDY SYNOPSIS (Continued)

Results:
(Continued)

Efficacy:

There was a statistically significant decrease in HIV-1 RNA at weeks 4 and 24 ($DAVG_4$ and $DAVG_{24}$) for all three doses of tenofovir DF compared to placebo. The greatest antiviral effect at weeks 4 and 24 was seen with the 300 mg dose of tenofovir DF ($p < 0.001$). The antiviral response occurred despite 94% of patients having HIV-1 with nucleoside resistance mutations at baseline. At week 24, 23% to 27% and 12% to 13% of the tenofovir DF-treated groups had viral loads under 400 and 50 copies/mL, respectively. Increases of 10 to 20 CD4 cells were seen in the tenofovir DF groups at week 48.

When the antiviral responses were analyzed by baseline genotype, significant decreases in HIV-1 RNA were obtained in the 300 mg dose group for patients with mutations associated with resistance to zidovudine, lamivudine, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). In all genotype groups, the antiviral effect was durable through 48 weeks.

At week 96 with all patients receiving open-label tenofovir DF 300 mg (from week 48) in combination with background antiretroviral therapy, the three originally randomized tenofovir DF groups achieved the antiviral response (≥ 0.62 $\log_{10}$ copies/mL reduction in HIV RNA from baseline) seen in the tenofovir DF 300 mg group at week 48.

Conclusions:

Through 24 weeks of treatment, the safety profile of tenofovir DF was similar to that of placebo. Through 48 weeks, there was no evidence of dose-related toxicity with tenofovir DF.

Tenofovir DF provided dose-related, durable reductions in HIV-1 RNA in highly treatment-experienced patients with evidence of nucleoside resistance. The greatest antiviral effect was associated with the use of tenofovir DF 300 mg once daily.

The long-term safety profile of tenofovir DF 300 mg in an open-label extended dosing phase is similar to that observed during the initial 48 weeks of the study.

NDA21-356 / SN

Section 3 Summary

GILEAD
Advancing Therapeutics.
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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products (HFD-530)
Attn:
9201 Corporate Boulevard
1st Floor Document Room
Rockville, MD 20850

Subject: **NDA 21-356 VIREAD® - Serial No. /Efficacy Supplement #01**
- **Clinical Study Reports 903, 907 and 919**

Reference is made to the letter approving NDA 21-356 in accordance with the regulations for accelerated approval (21 CFR 314.510) dated 26 October 2001 and the post-marketing commitments contained therein. In accordance with the obligations detailed in the approval letter, this efficacy supplement provides safety (including specialized bone evaluations) and efficacy data from antiretroviral-naïve patients (GS-99-903, 48-week data) and additional data in antiretroviral-experienced patients (GS-99-907, 48-week data). Pharmacokinetic data in subjects with renal insufficiency (Study GS-01-919) is also provided, along with a proposal for dosing interval adjustment based on renal function.

A revision to the approved package insert is proposed based on the data provided in this supplement (Sections 2). The proposed revision will be submitted under separate cover as a formal labeling supplement.

In accordance with the Prescription Drug User Fee Act (as amended by the Food and Drug Modernization Act of 1997), Gilead submitted on the use fee to support the review of this application. A copy of FDA Form 3397 and the accompanying proof of payment are enclosed in Section 18 of this application.

We respectfully request priority review of this efficacy supplement.

If you have any questions or need further information, please contact me at , or , , Regulatory Affairs, at .

Sincerely,

, Regulatory Affairs

Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
phone 650 574 3000 *facsimile* 650 578 9264
www.gilead.com