

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-356**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

**Medical Division:** Division of Antiviral Drug Products (HFD-530)

**Biometrics Division:** Division of Biometrics III (HFD-725)

NEW DRUG APPLICATION (NDA): 21-356

SERIAL NUMBER: 000

NAME OF DRUG: VIREAD™ 300 mg Tablets  
(tenofovir DF, tenofovir disoproxil fumarate,  
PMPA prodrug, TDF)

INDICATION: Treatment of HIV infection

APPLICANT: Gilead Sciences

DOCUMENTS REVIEWED: Submissions dated March 22, 2001 and  
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## STATISTICAL REVIEW AND EVALUATION

### A. Background

VIREAD™ (tenofovir disoproxil fumarate, tenofovir DF, PMPA prodrug) is the first drug in a new class of nucleotide reverse transcriptase inhibitors (NtRTI) (and as such distinct from nucleoside reverse transcriptase inhibitors [NRTIs]) developed for the treatment of human immunodeficiency virus type-1 (HIV-1) infection. Tenofovir DF is an ester prodrug of tenofovir (also known as PMPA) with activity *in vitro* against the HIV-1 and HIV-2 retroviruses. FDA designated this drug as a “fast track” drug product on May 1, 2001.

This is a priority review of the NDA 21-356, which seeks *accelerated approval* of tenofovir DF tablets for the treatment of HIV infection. In this submission, the efficacy results—of tenofovir DF administered in combination with other antiretroviral agents—are based on two placebo-controlled clinical trials (Studies 902 and 907) conducted in *treatment-experienced* HIV-1 infected patients with a detectable viral load (>400 copies/mL).

Study 902 is a phase 2 *dose-ranging study* of three doses of oral tenofovir DF tablets (75 mg, 150 mg, 300 mg) with *double-blind* placebo comparison data for 24 weeks, *double-blind* data from 24-48 weeks for tenofovir DF (75 mg, 150 mg, 300 mg) only and *open-label extended dosing* data beyond 48 weeks for tenofovir DF 300 mg alone. Study 907 is a *phase 3 study* of tenofovir DF 300 mg tablets compared to placebo, with data available for 24 weeks of *double blind* treatment. In both studies, an intensification strategy was used in which tenofovir DF was added to existing stable antiretroviral therapy in patients who had incomplete viral suppression (plasma HIV-1 RNA levels >400 copies/mL). (See Figure 1 for study designs.)

Additional data provided in this submission include data from five other clinical studies supporting the safety, clinical pharmacology and pharmacokinetics of oral tenofovir DF, and one clinical trial of intravenous (IV) tenofovir: Study 901 (phase 1/2), Study 908 (open-label safety), Study 909 (phase 1, healthy volunteers), Study 910 (open-label safety, extended dosing roll-over study from 901, 902, and 907, currently enrolling), Study 914 (phase 1, healthy volunteers), and Study 701 (phase 1 study of IV tenofovir).

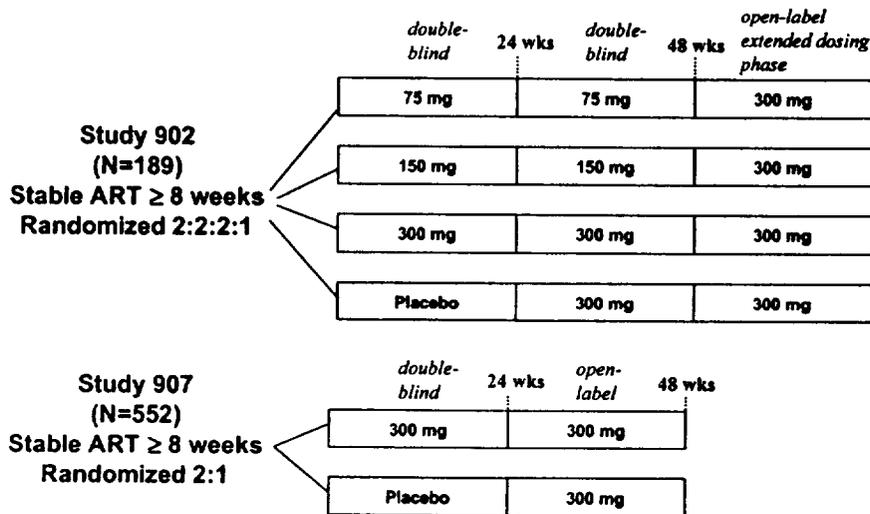
A currently ongoing phase 3 equivalence study in *treatment-naïve patients*, Study 903, described below will be submitted by the Applicant at a later time for review towards the *traditional approval* process. In addition, a second confirmatory study will also be conducted.

Study 903: 2 year, randomized, blinded study. Equivalence design with 600 antiretroviral naïve patients randomized 1:1 to d4T+3TC+efavirenz (or nevirapine) or tenofovir 300 mg+3TC+efavirenz (or nevirapine).

The focus of this statistical review will be data from two controlled efficacy studies; 902 and 907.

**B. Study Designs**

Studies 902 and 907 are both randomized, double-blind, placebo-controlled, multicenter studies to evaluate the antiviral efficacy of *tenofovir DF* in combination with other antiretroviral agents in extensively *treatment-experienced* HIV-infected patients with a detectable viral load (>400 copies/mL). A summary of the treatment schedule in these studies is shown in Figure 1 below.



Note: ART=AntiRetroviral Therapy

Source: Clinical Data Section of NDA

Figure 1: Treatment Schedule in Studies 902 and 907

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## 1. Protocol GS-98-902—Phase 2 Dose-Ranging 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”.  
[Study Period: 1) Blinded Phase—September 2, 1998 (first patient randomized) through March 16, 2000 (last patient observation); 2) Open-Label Phase—August 4, 1999 (first patient enrolled) through November 15, 2000 (last clinical observation)].

This is a dose-ranging study consisting of two phases: the *blinded phase* and the *open-label phase*. The *blinded phase* is a phase 2, randomized, double-blind, placebo-controlled dose ranging study for 24 weeks, designed to evaluate the safety and efficacy of three doses of tenofovir DF (75 mg, 150 mg, 300 mg) when administered in combination with other antiretroviral agents to treatment-experienced, HIV-infected patients. After 24 weeks, patients randomized to placebo are crossed-over to the tenofovir DF 300 mg group in a blinded manner. After 48 weeks of therapy, patients from the blinded phase receiving tenofovir DF 75 mg, 150 mg, or 300 mg are given the opportunity to receive tenofovir DF 300 mg in the *open-label phase* which is a non-randomized, single-arm study to evaluate the long-term safety and efficacy of tenofovir DF 300 mg.

### Population

The study was conducted in the United States (24 centers) in *treatment-experienced* HIV-infected patients of age 18-65 years who were receiving stable antiretroviral therapy—consisting of less than or equal to 4 active agents for  $\geq 8$  weeks—prior to study entry. Patients were to have viral load  $\geq 400$  but  $\leq 100,000$  (hundred thousand) plasma HIV-1 RNA copies/mL using the *standard assay* (Roche Amplicor HIV-1 Monitor™ Test).

### Sample Size

For the primary efficacy analyses, a total sample size of 175 subjects (50/arm for each of the three tenofovir DF groups and 25 in the placebo group) was determined to detect a difference of 0.25 (0.15 vs. 0.40) in DAVG of  $\log_{10}$  HIV-1 RNA levels between the tenofovir DF groups. A standard deviation of 0.4 (estimated from previous trials) and a dropout rate of 10% were assumed. This sample size would provide a statistical power of at least 80% to detect the difference in DAVG at a two-sided significance level of 0.05.

For the primary safety analyses, when a placebo is compared to a tenofovir DF group with respect to the proportion of patients with grade 3 or higher adverse events, a sample size of 25 patients in the placebo group vs. 50 patients in a tenofovir group would provide at least 80% power to detect a difference of 35% (10% vs. 45%) at a two-sided 0.05 level of significance. One of the goals of this study is to provide estimates of the adverse event rates in each group.

### Randomization

In addition to continuing their current antiretroviral regimen, a total of 175 patients were

to be randomized in a blinded fashion 2:2:2:1 to one of four treatment groups.

- 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 once daily (n=25)

Randomization of treatment will be balanced within site. Patients will be stratified according to three factors:

1. HIV-1 RNA level (<20,000 copies/mL or ≥20,000 copies/mL);
2. CD4 cell count (<200 or ≥200 cells/mm<sup>3</sup>); and
3. Number of prior antiretroviral drugs at the time of study entry (<4 or ≥4).

### Blinding

In the blinded phase, treatment will continue for 48 weeks during which both patients and providers will be blinded to treatment assignment. In the event of dose reduction due to toxicity, patients will be instructed to take the study drug once every other day following a meal and the tenofovir DF dose will remain blinded. At 24-weeks post-randomization, patients randomized to receive placebo will be crossed-over to blinded tenofovir DF 300 mg QD for the remainder of the 48-week period. Upon completion of 48-weeks on study, patients will be eligible to enter the open-label phase wherein patients will receive tenofovir DF 300mg once daily following a meal.

### Switching/Changing of background therapy

Patients will be encouraged to continue their baseline antiretroviral therapies, in addition to the assigned study drug, for at least 4 weeks post-randomization after which background antiretroviral therapy may be changed as desired while continuing the blinded study drug assignment. If the HIV RNA level for a patient remains above the limit of quantification at ≥12 weeks of therapy, a change in background antiretroviral therapy is strongly recommended.

### Efficacy Analysis

The co-primary efficacy endpoints are the *time-weighted change in log<sub>10</sub> HIV-1 RNA levels from baseline average* (i.e., geometric mean of RNA levels at pre-baseline and baseline visits) at Week 4 post-randomization (*DAVG4*) and at Week 24 post-randomization (*DAVG24*).

For evaluation of plasma HIV-1 RNA levels, the *standard assay* (i.e., Roche Amplicor HIV-1 Monitor™ Test, limit of detection [LOD]=400 copies/ml) will be used to determine the eligibility of patients at the screening visit. After screening, all evaluations of plasma HIV-1 RNA will be done using the *ultrasensitive assay* (i.e., Roche

UltraSensitive HIV-1 Monitor™ Test, LOD = 50 copies/ml).

The populations for the primary efficacy analysis will be both the ITT (Intent-To-Treat) and AT (As-Treated) populations. The *ITT* population will include all patients randomized and received at least one dose of study medication, with no data exclusions. Patients who receive study medication other than that intended or who receive no doses will be analyzed according to the group to which they were randomized. The *AT* population will include all patients who received at least one dose of study medication, excluding all data after permanent discontinuation of assigned treatment. Patients who receive study medication other than that intended will be analyzed according to study medication received.

Key treatment evaluations will include assessment of *plasma HIV RNA levels*, *CD4 cell counts*, *plasma bank* (for genotypic analyses of HIV-1 reverse transcriptase and protease gene mutations), and *bone densitometry* (at selected sites only). These evaluations will be performed at the following time points as shown in Table 1 below.

Table 1:  
 Treatment Evaluations and Time Points, Study 902

Time Point	Treatment Evaluations			
	Plasma HIV RNA	CD4 cell count	Plasma Bank	Bone Densitometry
<b>Blinded Phase</b>				
Screening		x		NA
Pre-baseline		NA		NA
Baseline		x		x †
End of Week		4, 8, 12, 24, and 36		12, 24, and 36 †
Week 48 or study drug discontinuation		x		x †
Follow-up §		x		NA
<b>Open-Label Extension Phase</b>				
Baseline ††		x		x †
Month 3, 6, 9, and quarterly thereafter		x		x
Final visit or study drug discontinuation		x		x
Follow-up §§		x		NA
NA = Evaluation not performed at this time point. † Plasma HIV-1 RNA will be evaluated at screening visit using the standard assay (Roche Amplicor HIV-1 Monitor test). Thereafter, for the remaining visits, the ultrasensitive assay (Roche UltraSensitive HIV-1 Monitor test) will be used. ‡ Bone densitometry test to be performed within a 1-week window (i.e., ±1 week). § Follow-up evaluation is performed 4 weeks after the last dose of study drug unless the patient enters the open-label phase within 1 month of Week 48 visit for blinded phase. †† Only evaluate a patient who's blinded phase Week 48 visit does not coincide with the Baseline visit for open-label phase. Patients for whom the Week 48 visit for the blinded phase coincides with the Baseline visit for the open-label phase will be dispensed open-label medication at that time. §§ Follow-up evaluation in open-label phase to be performed 1 month after the last dose of study drug.				

For the primary efficacy analysis, Wilcoxon rank-sum test (unstratified) will be used to compare the DAVG4 and DAVG24 between the treatment groups (pairwise comparisons). The DAVG4 and DAVG24 will be calculated as the time weighted change in  $\log_{10}$  HIV-1 RNA using the trapezoidal rule with all available windowed post-baseline data (data after initiation of study medication) minus the baseline average. No special handling of missing data will be done since the DAVG are based on all *available* data. A stratified Wilcoxon rank-sum test using the randomization strata will be conducted as a secondary analysis.

Additional analyses will be conducted on the following secondary efficacy endpoints:

- “Best response” to treatment, defined as the maximum decrease in HIV-1 RNA levels through Week 48 and time to best response.
- Time weighted change from baseline average in  $\log_{10}$  HIV-1 RNA levels at Week 12 (DAVG12) and at Week 48 (DAVG48).
- Proportion of patients with  $\geq 0.5$   $\log_{10}$  decrease in HIV-1 RNA levels at Weeks 4, 24, and 48.
- Proportion of patients with  $\geq 1$   $\log_{10}$  decrease in HIV-1 RNA levels at Weeks 24, and 48.
- Proportion of patients with plasma HIV-1 RNA levels below the lower limit of quantification (i.e.,  $< 50$  copies/mL using Ultrasensitive HIV-1 Monitor™ test) at Weeks 4, 12, 24, and 48 and time to HIV-1 RNA  $< 50$  copies/mL.
- Proportion of patients with plasma HIV-1 RNA levels  $< 400$  copies/mL at Weeks 4, 12, 24, and 48 and time to HIV-1 RNA  $< 400$  copies/mL.
- Change in CD4 cell count from baseline during the study period

The continuous endpoints including *best response to treatment* and *DAVG* will be compared between treatment groups using the Wilcoxon rank-sum test. The discrete endpoints including the *proportion* endpoints will be compared between the treatment groups using the Cochran Mantel-Haenszel test. The endpoints on *time to event* will be estimated using the Kaplan-Meier method and compared between treatment groups using the log-rank test. *Change in CD4 cell count* from baseline will be summarized by treatment group for each study visit.

The protocol was finalized on May 10, 2000 (Amendment 5). The last patient observation for the blinded phase was on March 16, 2000 and the last clinical observation for the open-label phase was on November 15, 2000.

## 2. Protocol GS-99-907—Phase 3 Placebo-Controlled Study

Title: “A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of the Safety and Efficacy of Tenofovir Disoproxil Fumarate in Combination With Other Antiretroviral Agents for the Treatment of HIV-1-Infected Patients”. [Study Period: November 30, 1999 (first patient randomized) through current. Last patient randomized at June 12, 2000. Data set analyzed for all patient observations through November 30, 2000]

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the antiviral activity (efficacy), safety and tolerability of tenofovir DF 300 mg once daily versus placebo when added to stable antiretroviral therapy (i.e., intensification strategy) in treatment-experienced HIV-1 infected patients who have viral load between 400 and 10,000 plasma HIV-1 RNA copies/mL using the Roche Amplicor Monitor™ UltraSensitive Test.

### Population

The study was conducted at 72 centers in the United States (55), Europe (15), and Australia (2). The patient population for this study were *treatment-experienced* HIV-infected patients of age 18-65 years who were receiving stable antiretroviral therapy—consisting of  $\leq 4$  antiretroviral agents for at least 8 weeks—prior to randomization. Patients were to have plasma HIV-1 RNA levels  $\geq 400$  but  $\leq 10,000$  (ten thousand) copies/mL using the *ultrasensitive assay* (Roche Amplicor HIV-1 Monitor™ Ultrasensitive Test, Version 1.0, lower limit of quantification [LLOQ]=50 copies/mL). For non-U.S. sites only, both versions, Version 1.0 and 1.5, of the *ultrasensitive assay* (Roche Amplicor HIV-1 Monitor™ Ultrasensitive Test Version 1.0 and Version 1.5, LLOQ=50 copies/mL) will be used at screening for all patients.

### Sample Size

A total of 600 patients were planned to detect a treatment difference between tenofovir DF and placebo in  $DAVG_{24}$  of 0.25  $\log_{10}$  plasma HIV-1 RNA copies/ml using the Wilcoxon rank sum test and assuming a standard deviation in  $DAVG_{24}$  of 0.75, statistical power of 90%, two-sided 0.05 level of significance and 10% patients lost-to-follow.

### Randomization

In addition to continuing their existing antiretroviral therapy, a total of 600 patients were to be randomized in a blinded fashion 2:1 to one of the two treatment groups.

Group 1: Tenofovir DF 300 mg once daily (n=400)

Group 2: Placebo once daily (n=200)

Patients will be stratified according to three parameters:

1. HIV-1 RNA level (<5,000 copies/mL or ≥5,000 copies/mL);
2. CD4 cell count (<200 or ≥200 cells/mm<sup>3</sup>); and
3. Number of prior antiretroviral drugs at the time of study entry (<4 or ≥4).

### Blinding

Tenofovir DF (TDF) supplied as 300 mg tenofovir DF tablets and the matching TDF placebo will be supplied to the patients for the first 24 weeks of the study in a blinded fashion. At 24 weeks post-randomization, patients randomized to receive placebo will be crossed over to receive active TDF 300 mg once daily for the remainder of the 48-week study. At the end of Week 48, patients without dose-limiting toxicity will have the option to participate in the rollover protocol, GS-99-910, where they will continue to receive TDF until it is commercially available or Gilead Sciences terminates the study.

### Switching/Changing of background therapy

Patients and physicians will be strongly discouraged from changing their baseline antiretroviral therapy, in addition to the assigned study drug, during the blinded phase (i.e., for at least 24 weeks post-randomization). Thereafter, changes in background antiretroviral therapy may be made as desired while continuing tenofovir DF.

### Efficacy Analysis

The primary efficacy endpoint is the *time-weighted change in log<sub>10</sub> HIV-1 RNA levels from baseline average* (i.e., geometric mean of Pre-Baseline and Baseline visits) at Week 24 post-randomization (*DAVG<sub>24</sub>*).

The primary population for the efficacy analyses will be the ITT (intent-to-treat) population. The ITT population includes all patients randomized and who receive at least one dose of study medication. Patients with major eligibility violations that are identifiable based on pre-randomization characteristics will be excluded. All patients will be analyzed according to the group to which they were randomized regardless of whether or not they receive the study medication that was intended.

The AT (as-treated) population will be also be used for analysis of efficacy endpoints. The AT population includes all patients who receive at least one dose of study drug and have not committed any major protocol violations. Data collected after patients received new antiretrovirals, which was not received at baseline during the first 24 weeks of the study will be excluded from this analysis. Patients who receive study medication other than that intended will be analyzed according to the therapy received.

For the primary efficacy analysis, the treatment groups (TDF 300 mg vs. placebo) will be compared using *DAVG<sub>24</sub>* by a two-sided Wilcoxon rank-sum test (unstratified) at a two-sided 0.05 level of significance. *DAVG<sub>24</sub>* is defined as the time-weighted average

between the first post-baseline value through the last available value up to Week 24 minus the baseline value. The baseline value is defined as the geometric mean of the pre-baseline and baseline plasma HIV-1 RNA values. If one of the two values is missing, then the non-missing value will be used. For placebo crossover to tenofovir DF (open-label), the baseline HIV-1 RNA is defined as the last non-missing HIV-1 RNA on or prior to the first open-label study drug.

A variety of secondary analyses on the primary efficacy endpoint of  $DAVG_{24}$  will also be performed. These will include: (1)  $DAVG_{24}$  computed only while patients remain on blinded therapy, (2) change in  $\log_{10}$  RNA levels between baseline and the time at which either study drug is discontinued and/or there is change in background therapy, (3)  $DAVG_{24}$  analyses within subgroups defined by stratification factors, and (4) van Elteren's test of the treatment effect on  $DAVG_{24}$  adjusted for the three stratification factors.

Additional analyses will be performed on the following secondary efficacy endpoints:

- Proportion of patients with HIV-1 RNA  $\leq 50$  and  $\leq 400$  copies/mL at Weeks 16, 24, and 48 using the ultrasensitive assay.
- $DAVG$  (time-weighted average) through Week 48 for  $\log_{10}$  plasma HIV-1 RNA
- Changes in CD4 cell count over time.
- Development of HIV-1 resistance and the role that baseline mutations have with regard to antiviral response in a subset of patients.
- Change in HIV-1 RNA and CD4 for placebo patients who cross over to open label TDF from Week 24.
- Time to increase in viral load  $> 400$  copies/mL for patients achieving loads  $\leq 400$  copies/mL, and again for all patients.

#### Treatment Evaluations and Assay

The following key treatment evaluations will be performed at Screening, Pre-baseline, Baseline and Week 48 (or study drug discontinuation): CD4 cell count; Plasma HIV-1 RNA (Roche Amplicor Monitor™ Ultrasensitive Test); and Plasma bank.

During Weeks 1-44, treatment evaluations will be performed at the following time points.

- CD4 cell count (Weeks 4, 8, 12, 16, 20, 24, 32, and 40)
- Plasma HIV-1 RNA (Ultrasensitive assay, Weeks 2, 4, 8, 12, 16, 20, 24, 32, and 40)
- Plasma bank (Weeks 4, 8, 12, 16, 20, 24, 32, and 40)
- Bone densitometry (Week 24, at selected US sites only)

Bone densitometry will also be performed at Week 48 at selected sites only.

After the last study visit, all patients will require a 30-day follow-up visit. However, for patients who choose to participate in the open-label phase, i.e., in the rollover Protocol

910, a 30-day follow-up visit will not be required and the Week 48 visit will count as the Entry visit for Protocol 910. Patients who discontinue treatment prior to Week 48 will have study drug discontinuation visit and follow-up visits.

All laboratory samples will be sent to a central laboratory. Plasma HIV-1 RNA levels will be assessed throughout the study using the ultrasensitive assay.

For U.S. sites, Version 1.0 of Roche Amplicor Monitor™ Ultrasensitive Test (LLOQ=50 copies/mL) will be used at screening and all remaining visits.

For non-U.S. sites, both Version 1.0 and 1.5 of Roche Amplicor Monitor™ Ultrasensitive Test (LLOQ=50 copies/mL) will be used at the Screening visit. If the results from both tests differ by  $0.7 \log_{10}$  and the result of Version 1.5 is greater, then Version 1.5 will be used to measure HIV-1 RNA levels at the subsequent visits. For patients with  $<0.7 \log_{10}$  difference in the two test results, Version 1.0 assay will be used throughout the study. For patients who have the screening results from both Versions 1.0 and 1.5, the HIV-1 RNA result of the version which is also used at all the subsequent visits will be chosen in the analysis. In the cases where the viral load is greater than the upper limit of quantification (ULOQ) of the Roche Amplicor HIV-1 Monitor™ Ultrasensitive Method (ULOQ=75,000 copies/mL), the Roche Amplicor HIV-1 Monitor™ Test (standard assay) will be subsequently used.

The protocol was finalized on October 9, 2000 (Amendment 3) and the data cut off included all patient observations through November 30, 2000.

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## C. Applicant's Results

### 1. Demographics and Baseline Characteristics

Both studies 902 and 907 enrolled *treatment-experienced* HIV-infected patients who were receiving stable antiretroviral therapy consisting of  $\leq 4$  antiretroviral agents for at least 8 weeks prior to randomization. The studies differed in terms of the entry criteria for the patients with respect to the baseline viral load: Patients in Study 902 could have higher baseline viral load ( $\leq 100,000$  [hundred thousand] plasma HIV-1 RNA copies/mL) than in Study 907 ( $\leq 10,000$  [ten thousand] copies/mL).

Table 2 compares the demographics and baseline characteristics of the subjects in the two studies.

As shown in Table 2, the size of Study 907 (N=550 patients) was approximately three times as big as Study 902 (N=186). Studies 902 and 907 were similar in terms of patient demographics such as age, weight, gender and race. The median age of patients was approximately 40 years in both studies. The patients were predominantly males (92% in Study 902 and 85% in Study 907). Majority of the patients were White.

The studies were also similar in terms of baseline characteristics such as median baseline viral load, median CD4+ cell counts (majority had  $\geq 200$  cells/mm<sup>3</sup> at baseline), and number of prior antiretroviral therapies. Patients in both studies had substantial prior exposure to antiviral therapies. Majority of them had used 4 or more antiretrovirals. The median duration of prior antiretroviral use was 4 years in Study 902 and approximately 5 years in Study 907.

The studies differed in terms of route of HIV transmission and CDC classification.

- A higher proportion of patients had acquired the disease through homosexual contact in Study 902 (82%) than in Study 907 (69%), and a higher proportion of patients had acquired HIV through IV drug use in Study 902 (10%) than in Study 907 (6%).
- More patients in Study 902 were in an advanced stage of the disease than in Study 907 in terms of CDC classification. Approximately half of the patients in Study 902 had AIDS (CDC class C events) and the other half had either symptomatic events or were asymptomatic. In contrast, in Study 907 approximately half of the patients were asymptomatic and the remaining had either symptomatic or CDC class C (AIDS) events.

Table 2: Demographics and Baseline Characteristics by Study (Intent-to-Treat Population)

Characteristic		Study	
		902 N=186	907 N=550
<b>Age (years)</b>	Median (Range)	41 (27 to 62)	40 (22 to 70)
<b>Weight (kg)</b>	Median	78	77
<b>Gender</b>	Male	92%	85%
	Female	8%	15%
<b>Race</b>	White	74%	69%
	Black	13%	17%
	Hispanic	11%	12%
	Native American	1%	—
	Asian	—	<1%
	Other	1%	2%
<b>Route of HIV Transmission †</b>	Homosexual contact	82%	69%
	Heterosexual contact	13%	27%
	IV drug use	10%	6%
	Transfusion	3%	3%
	Other	2%	3%
	Unknown	—	2%
<b>HIV-1 Status (CDC Classification)</b>	A: Asymptomatic	38%	50%
	B: Symptomatic HIV infection	15%	23%
	C: AIDS	47%	27%
<b>Baseline HIV-1 RNA (copies/mL)</b>	Mean	4,571	2,291
	Median	5,012	2,344
<b>Baseline HIV-1 RNA (log<sub>10</sub> copies/mL)</b>	Median (Range)	3.7 [redacted]	3.4 [redacted]
<b>Baseline CD4+ cell count (cells/mm<sup>3</sup>)</b>	Mean	374	427
	Median (Range)	331 [redacted]	386 [redacted]
<b>Duration of HIV Infection</b>	Median	7 yrs 11 mos	—
<b>Duration of Prior Antiretroviral use</b>	Median	4 yrs	4.9 yrs
<b>SUBGROUPS</b>			
<b>Baseline plasma HIV-1 RNA</b>	< 5,000 copies/mL	51%	78%
	≥ 5,000 copies/mL	49%	22%
<b>Baseline plasma HIV-1 RNA</b>	< 20,000 copies/mL	84%	—
	≥ 20,000 copies/mL	16%	—
<b>Baseline CD4+ cell count</b>	< 200 cells/mm <sup>3</sup>	22%	13%
	≥ 200 cells/mm <sup>3</sup>	78%	87%
<b>Prior Antiretroviral Use</b>	< 4 therapies	21%	20%
	≥ 4 therapies	79%	80%

† Patients may have contracted HIV through more than one route of transmission. Percentages will not add to 100.

Source: Tables 4, 7, 8, 11, 12.12 and 12.13 of Volume 1.004 for Study 902. Tables 2, 3, 4, 5, and 30 of Volume 3.85 for Study 907.

**2. Subject Accounting**

Table 3 shows the disposition of patients through 24 weeks of treatment for the two pivotal studies.

Table 3:

Subject Accounting Through Week 24  
 by Study and Treatment Group

Number of Subjects	Study 902 N=189				Study 907 N=552	
	Placebo	Tenofovir DF			Placebo	Tenofovir DF 300 mg
		75 mg	150 mg	300 mg		
Total Randomized	28 (100%)	54 (100%)	51 (100%)	56 (100%)	184 (100%)	368 (100%)
Randomized but not treated †	0 (0%)	1 (2%)	0 (0%)	2 (4%)	2 (1%)	0 (0%)
Treated ‡	28 (100%)	53 (98%)	51 (100%)	54 (96%)	182 (99%)	368 (100%)
Completed study through Week 24	21 (75%)	48 (89%)	43 (84%)	48 (86%)	171 (93%)	345 (94%)
Discontinued study prior to Week 24	7 (25%)	5 (9%)	8 (16%)	6 (11%)	11 (6%)	23 (6%)
Reason discontinued						
Adverse event/Intercurrent Illness	1 (4%)	2 (4%)	5 (10%)	2 (4%)	5 (3%)	11 (3%)
Withdrawn consent	- -	- -	- -	- -	2 (1%)	1 (0%)
Loss to follow	2 (7%)	1 (2%)	2 (4%)	1 (2%)	2 (1%)	6 (2%)
Lack of virologic response	2 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Pregnancy	- -	- -	- -	- -	1 (1%)	1 (0%)
Death	0 (0%)	1 (2%)	0 (0%)	0 (0%)	- -	- -
Other §	2 (7%)	1 (2%)	1 (2%)	3 (5%)	0 (0%)	4 (1%)

Percentages in the table are calculated based on the total number of randomized subjects in each group. A “-” entry in table indicates no data for that category in that study.

Number of study centers = 22 in United States in Study 902 and 72 in Study 907 (52 in United States, 15 in Europe and 2 in Australia. Three sites received drug but never enrolled).

† Randomized-but-not-treated patients were randomized but did not receive any study medication.

‡ Treated patients received at least one dose of study medication.

§ Other category includes noncompliance, protocol violation and other reasons

Source: Table 5 of Volume 1.004 for Study 902. Tables 1, 8 and 9 of Volume 3.85 for Study 907.

In Study 902, a total of 189 subjects were randomized, among which only three patients (1 in TDF 75 mg group and 2 in TDF 300 mg) were never treated (did not receive any study drug). Therefore the ITT (Intent-to-Treat) population was smaller than the randomized population and consisted of 186 subjects (n=28 for Placebo, 53 for 75mg, 51 for 150mg, and 54 for 300mg Tenofovir DF) who were randomized and treated (received at least one dose of study medication). As planned per protocol 902, the placebo group had approximately half as many randomized patients as in each of the Tenofovir DF groups. A total of 160 patients completed the first 24-week blinded phase of the study, while 26 patients discontinued the study prior to 24 weeks. The premature discontinuation rates (prior to Week 24) were higher in the placebo arm (7/28=25%) than in each of the Tenofovir DF groups (5/54=9% in 75mg, 8/51=16% in 150mg, and 6/56=11% in 300mg), but the differences were not statistically significant. The number of discontinuations due to adverse events were generally similar among placebo, TDF 75mg, and TDF 300mg groups, whereas the TDF 150 mg group had a higher rate (5/51=10%) of discontinuation due adverse events. These differences were not statistically significant. One patient died in the TDF 75 mg group due to suicide through an intentional drug overdose (non-study drug).

In Study 907, a total of 552 patients were randomized to treatment with 368 randomized to Tenofovir DF 300 mg and 184 to placebo (in a 2:1 ratio as planned). Two patients in the placebo group were never treated. Therefore the ITT population consisted of 550 patients (182 in placebo and 368 in TDF 300mg) who were randomized and treated (received at least one dose of study drug). Majority of the patients (n=516) completed the first 24-week blinded study period while 34 patients discontinued prior to 24 weeks. The discontinuation rates due to various reasons were similar between the two groups.

Both studies continued beyond 24 weeks through 48 weeks (see Figure 1). Study 902 remained *blinded from Week 24 through 48* during which all patients randomized to Placebo were to cross-over to Tenofovir DF 300 mg. Of the 28 patients originally randomized to placebo, 21 crossed-over to TDF 300mg after Week 24 and the remaining 7 had discontinued prior to Week 24. Study 907 was *open-label after Week 24* after which all patients (originally randomized to Placebo or Tenofovir DF 300mg) were to roll-over to Tenofovir DF 300mg.

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### 3. Efficacy Analyses

The primary efficacy variable for both Study 902 and 907 was the *time-weighted change from baseline in log<sub>10</sub> HIV-1 RNA levels (DAVG)*. Efficacy was evaluated at Weeks 4 and 24 for Study 902 and at Week 24 for Study 907. The population for the primary efficacy analyses in both studies was the *intent-to-treat (ITT)* population that consisted of all patients randomized who received at least one dose of study medication.

The primary efficacy results are shown in Table 4.

Table 4:  
 Time-weighted change from baseline (DAVG<sub>xx</sub>) in log<sub>10</sub> HIV-1 RNA levels  
 by Study and Treatment Group  
 (ITT Population)

Study	Treatment Group / Week		n	DAVG <sub>xx</sub>		DAVG <sub>xx</sub> Median	p-value (TDF vs. Placebo)
				Mean	(SD)		
Study 902 (N=186)	Placebo	Week 4	28	0.02	(0.39)	-0.04	—
		Week 24	28	0.02	(0.69)	0.04	—
		Week 48	—	—	—	—	—
	TDF 75 mg	Week 4	53	-0.22	(0.35)	-0.14	0.008
		Week 24	53	-0.26	(0.51)	-0.16	0.013
		Week 48	53	-0.33	(0.59)	-0.29	—
	TDF 150 mg	Week 4	50	-0.44	(0.42)	-0.36	<0.001
		Week 24	51	-0.34	(0.59)	-0.23	0.002
		Week 48	51	-0.34	(0.59)	-0.29	—
	TDF 300 mg	Week 4	54	-0.62	(0.49)	-0.56	<0.001
		Week 24	54	-0.58	(0.63)	-0.54	<0.001
		Week 48	54	-0.62	(0.63)	-0.61	—
Placebo cross-over to 300mg (24-48 weeks)	Week 4	—	—	—	—	—	
	Week 24	—	—	—	—	—	
	Week 48	21	-0.52	(0.90)	-0.38	—	
Study 907 (N=550)	Placebo	Week 4	182	-0.03	(0.36)	-0.00	—
		Week 24	182	-0.03	(0.36)	-0.02	—
	TDF 300 mg	Week 4	366	-0.60	(0.57)	-0.55	<0.0001
		Week 24	367	-0.61	(0.61)	-0.56	<0.0001
		Week 48	368	-0.61	(0.61)	-0.56	—

N = Total number of subjects in the study in the ITT population.  
 n = Number of patients in each treatment group.

Table 4:

Time-weighted change from baseline (DAVG<sub>xx</sub>) in log<sub>10</sub> HIV-1 RNA levels  
by Study and Treatment Group  
(ITT Population)

p-value compares TDF groups versus Placebo based on unstratified Wilcoxon rank-sum test.

NOTE: Primary endpoint was evaluated at Weeks 4 and 24 in Study 902 and at Week 24 in Study 907.  
In Study 902, patients randomized to Placebo crossed-over to blinded TDF 300mg after Week 24.  
Study 902 was blinded through Week 48. Study 907 was blinded through Week 24 and open-label  
from 24-48 weeks.

Source: Table 12.11 in Volume 1.004 of 902 Study Report. Table 19 and 19.2 in Volume 3.85 of 907 Study  
Report.

The applicant concluded that there was a statistically significant decrease in the viral load from baseline at 4 weeks (DAVG<sub>4</sub>) and 24 weeks (DAVG<sub>24</sub>) in patients treated with tenofovir DF (either 75mg, 150mg, or 300mg QD) as compared to the placebo-treated patients, based on Study 902. Recall that these patients were receiving stable antiretroviral therapy with sub-optimal virological suppression prior to study entry.

Based on Study 907, the applicant also concluded that the time-weighted mean change from baseline in viral load was significantly greater in the tenofovir DF 300mg QD group (-0.61 log<sub>10</sub> HIV-1 RNA copies/mL) than that seen in the placebo group (-0.03 log<sub>10</sub> HIV-1 RNA copies/mL) after 24 weeks of treatment.

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Other secondary endpoints that were evaluated at Week 24 included the *proportion of patients with plasma HIV-1 RNA  $\leq 400$  copies/mL and  $\leq 50$  copies/mL*, as well as the *median change from baseline in CD4+ cell counts*.

Table 5 shows the secondary efficacy analysis results with respect to the proportion endpoints evaluated at Week 24 for Study 902 and 907.

Table 5:

Proportion of Patients with Plasma HIV-1 RNA  $\leq 400$  copies/mL or  $\leq 50$  copies/mL at Week 24, by Study and Treatment Group (ITT Population)  
 (Scenario: Missing = Failures)

Study		Treatment Group			
		Placebo n=28	75 mg n=53	150 mg n=51	300 mg n=54
902	Success criteria		Tenofovir DF		
	$\leq 400$ copies/ml	6 (21%)	12 (23%)†	14 (27%)†	14 (26%)†
	$\leq 50$ copies/ml	3 (11%)	7 (13%)†	6 (12%)†	7 (13%)†
907		Placebo n=182	Tenofovir DF 300 mg n=368		
	$\leq 400$ copies/ml	23 (13%)	155 (42%)		
	$\leq 50$ copies/ml	2 (1%)	76 (21%)		
	p-value	<0.0001*			
LOQ = Limit of Quantification of assay. Ultrasensitive assay was used for both studies. NOTE: The applicant considered the patients with viral load equal to 400 copies/mL or equal to 50 copies/mL as successes. These are typically evaluated (in other HIV clinical trials) as failures. p-value is based on the Cochran-Mantel-Haenszel test for general association. † No statistically significant difference observed between Tenofovir DF groups and Placebo group. * Statistically significant for both success criteria (i.e., $\leq 400$ copies/mL and $\leq 50$ copies/mL) at two-sided $\alpha = 0.05$					

Source: Table 13.11 of Volume 1.004 for Study 902. Table 22.1 of Volume 3.85 for Study 907.

As shown in Table 5, there was no statistically significant difference in proportion of successes (viral load below or equal to 400 copies/mL or 50 copies/mL) between the tenofovir DF groups and placebo. However, in the larger study (907), a statistically significant difference was observed in the proportion of successes in the tenofovir DF 300 mg group versus placebo. A total of 42% (155/368) of patients had a viral load suppression below or equal to 400 copies/mL at Week 24 and 21% (76/368) were suppressed below or equal to 50 copies/mL. Note that this analysis was based on the snapshot data of Week 24 only.

In Table 6 and Table 7 the median change from baseline in CD4+ cell counts over the course of Study 902 and Study 907, respectively, are summarized.

Table 6:

Summary of Median Change from Baseline in CD4+ Cell Counts  
 by Study Visit—Study 902 (ITT Population)

Treatment Week	Placebo		Tenofovir DF						Placebo cross-over to 300 mg (24-48 weeks)	
			75 mg		150 mg		300 mg			
	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>
Baseline Median	28	250.0	53	343.0	51	380.0	54	298.0	21	316.0
Week 4	26	-9.5	51	-1.0	48	-1.5	51	+14.0	—	—
Week 8	28	+5.5	51	+9.0	47	-4.0	50	-2.0	—	—
Week 12	27	-10.0	51	-25.0	47	-36.0	53	-4.0	—	—
Week 24	22	+20.5	50	+12.0	46	-7.0	50	-3.5	3	-28.0
DAVG24 [mean (std)]	28	-3.6 (80.0)	53	1.8 (84.0)	51	-11.3 (81.4)	54	-10.5 (80.6)		
Week 36	1	-186.0	46	+7.5	40	-8.0	45	+22.0	21	+12.0
Week 48	1	-97.0	42	-13.5	36	+24.5	43	+12.0	18	+3.5

n = Number of patients remaining at each week.  
 NOTE: Patients randomized to the placebo group cross-over to blinded TDF 300mg after Week 24.  
 + or - sign indicates median increase or decrease in CD4+ cell count compared to baseline.  
 — indicates not applicable.

Source: Table 22 and 24 of 902 Clinical Study Report.

### Statistical Reviewer's Comments

The applicant performed pairwise comparisons between all treatment groups in Study 902 (p-values not shown in Table 6) and found no statistically significant differences in the median change from baseline in CD4+ cell counts at any pretreatment or on-treatment time point.

As shown in Table 6, there is no consistent pattern over time of either median increase or decrease in CD4+ cell counts in any of the tenofovir DF treatment groups. At Week 24, there was no significant difference between tenofovir DF (either 75mg, 150mg, or 300mg) and placebo. After Week 24, patients randomized to placebo rolled-over to blinded tenofovir DF 300mg. At Week 48, patients randomized to the TDF 75 mg group had a median change from baseline in CD4+ cell count of -13.5 cells/mm<sup>3</sup>, while the 150 mg and 300 mg groups showed a median increase of +24.5 and +12.0 cells/mm<sup>3</sup>, respectively.

Table 7:

Summary of Median Change from Baseline in CD4+ Cell Count  
 by Study Visit—Study 907 (ITT Population)

Treatment Week	Placebo		Tenofovir DF 300 mg		Placebo cross-over to 300 mg (open-label) (24-48 weeks)		p-value (TDF vs. Placebo) (0-24 weeks)
	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>	n	Cells/mm <sup>3</sup>	
Baseline Median	182	417.3	368	376.0	170	409.5	0.190
Week 4	177	-11.5	352	+3.5			0.017
Week 8	172	-3.0	356	+7.0			0.048
Week 12	175	-13.5	352	+8.5			0.003 *
Week 16	170	-13.8	347	+10.0			0.035
Week 20	169	-6.0	346	+12.3			0.032
Week 24	170	-2.8	336	+6.0			0.178
<b>DAVG<sub>24</sub></b> <b>[mean (std)]</b>	<b>182</b>	<b>-10.6 (88.4)</b>	<b>367</b>	<b>+12.6 (78.4)</b>			<b>0.001**</b>
Week 32			217	+14.5	112	+11.5	
Week 40			81	+5.5	37	+11.0	
Week 48			22	-35.8	13	+67.0	

p-values based on Wilcoxon rank-sum test for comparing medians of two groups.  
 Note: For placebo cross-over group, change in CD4 cell count from Week 24 is shown.  
 \* Statistically significant at  $\alpha = 0.05/7 = 0.007$  after adjusting for multiple comparisons. Other p-values not statistically significant.  
 \*\* DAVG<sub>24</sub> statistically significant at  $\alpha=0.05$ .

Source: Table 28, 28.2, and 29 of Volume 3.85 of 907 Study Report.

### Statistical Reviewer's Comments

Throughout the Clinical Study Reports of 902 and 907, the applicant compares the viral load and CD4+ cell counts in the tenofovir DF groups with the placebo group in terms of means. However, the p-values reported are based on the Wilcoxon rank-sum test that compares medians between the two groups. Comparison of medians is a more robust comparison when the data is skewed. Therefore, the FDA reviewer has presented information in tables in terms of medians.

As shown in Table 7, in Study 907, after adjusting for multiplicity ( $\alpha/7=0.007$ ) there was a statistically significant difference in *median change from baseline in CD4+ cell counts* only at Week 12 in favor of tenofovir DF (+8.5 cells/mm<sup>3</sup>) as compared to the placebo group (-13.5 cells/mm<sup>3</sup>). There was no statistically significant difference at any other time

point up to Week 24 between tenofovir DF and placebo. However, the time-weighted average of the CD4+ cell counts at Week 24,  $DAVG_{24}$ , was significantly different from Placebo in favor of Tenofovir DF which reflected a consistent overall pattern of a modest gain of CD4 cells in the TDF arm versus the Placebo arm.

After Week 24, since all patients were given open-label tenofovir DF 300mg, comparisons cannot be made between tenofovir DF and placebo. At Week 48, CD4+ cell count data was available only in 22 patients receiving tenofovir DF. This showed a median decrease from baseline of  $-35.8$  cells/mm<sup>3</sup>.

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#### 4. Subgroup Analyses for Efficacy

Subgroup analyses were conducted on the primary efficacy endpoint (DAVG<sub>xx</sub> in log<sub>10</sub> HIV-1 RNA levels) in both studies by the following patient subgroups.

- Baseline HIV-1 RNA  $\leq 5,000$  copies/mL versus  $> 5,000$  copies/mL
- Number of prior antiretroviral medications in the baseline background therapy  $< 4$  versus  $\geq 4$ .

In Study 907, efficacy was also evaluated for patients with baseline CD4+ cell count  $< 200$  cells/mm<sup>3</sup> versus  $\geq 200$  cells/mm<sup>3</sup>.

These results are shown in Table 8 and Table 9.

##### Statistical Reviewer's Comments

As shown in Table 8, in both studies, there was a statistically significant net reduction in viral load at Week 24 (in terms of DAVG<sub>24</sub> in log<sub>10</sub> HIV-1 RNA levels) favoring tenofovir DF 300 mg versus placebo in the above subgroups, except the subgroup of patients who had baseline viral load  $\geq 5,000$  copies/mL in Study 902.

In Study 907, in the patients with baseline viral load  $\geq 5,000$  copies/mL, a significant difference was observed in median DAVG<sub>24</sub> in the tenofovir 300 mg group (n=99) versus the placebo (n=43) group (-0.57 vs. -0.14 log<sub>10</sub> HIV-1 RNA copies/mL at Week 24). However, in Study 902, there was no significant difference between tenofovir 300mg (n=26, median DAVG<sub>24</sub> = -0.26) vs. placebo (n=18, median DAVG<sub>24</sub> = 0.00) with a p-value of 0.063.

With respect to the secondary endpoints of *proportion of patients with viral load  $\leq 400$  copies/mL (or  $\leq 50$  copies/mL) at Week 24* (scenario: missing=failures, i.e., missing observations treated as having viral  $>$ specified level of 400 copies/mL or 50 copies/mL), patients in Study 902 with baseline viral load either  $< 5,000$  or  $\geq 5,000$  copies/mL did not show any significant difference between the TDF 300mg and placebo groups (see Table 9 and Table 10).

In Study 907, there was no significant difference between TDF 300 mg and Placebo in terms of the proportion of patients who achieved  $\leq 50$  copies/mL at Week 24 and had baseline viral load  $\geq 5000$  copies/mL.

For the remaining subgroup of patients, the treatment effect favored tenofovir DF 300 mg as compared to placebo.

Table 8:

Time-Weighted Change from Baseline (DAVG<sub>24</sub>) in log<sub>10</sub> HIV-1 RNA at Week 24  
 by Randomization Strata—Study 902 and 907 (ITT Population)

Randomization Strata / Subgroup	DAVG <sub>24</sub> Viral Load	Study 902				Study 907			
		TDF 300 mg (n=54)	Placebo (n=28)	Treatment Effect (TDF-PLA)	p-value	TDF 300 mg (n=368)	Placebo (n=182)	Treatment Effect (TDF-PLA)	p-value
Plasma HIV-1 RNA <5,000 copies/mL	n	28	10			268	139		
	Mean (SD)	-0.68 (0.54)	+0.33 (0.53)	-1.01	<0.001 *	-0.59 (0.61)	+0.03 (0.33)	-0.62	<0.0001 *
≥5,000 copies/mL	n	26	18			99	43		
	Mean (SD)	-0.47 (0.70)	-0.16 (0.72)	-0.31	0.063 †	-0.67 (0.61)	-0.22 (0.38)	-0.45	<0.0001 *
CD4 <200 cells/mm <sup>3</sup>	n	15	7			45	21		
	Mean (SD)	-0.24 (0.42)	+0.33 (0.31)	-0.57	<0.001 *	-0.39 (0.55)	+0.05 (0.37)	-0.44	0.0007 *
≥200 cells/mm <sup>3</sup>	n	39	21			322	161		
	Mean (SD)	-0.71 (0.65)	-0.09 (0.76)	-0.62	0.002 *	-0.64 (0.61)	-0.04 (0.35)	-0.60	<0.0001 *
Prior ARV use <4 drugs	n	33	17			62	33		
	Mean (SD)	-0.59 (0.61)	-0.24 (0.69)	-0.35	0.040 *	-0.89 (0.54)	-0.09 (0.33)	-0.80	<0.0001 *
≥4 drugs	n	21	11			305	149		
	Mean (SD)	-0.56 (0.67)	0.41 (0.49)	-0.97	<0.001 *	-0.56 (0.61)	-0.02 (0.36)	-0.54	<0.0001 *

Note: P-values compare TDF 300 mg vs. Placebo. P-value for DAVG<sub>24</sub> is based on the Wilcoxon rank sum test for comparing medians.

\* p-value is statistically significant at  $\alpha=0.05$  after adjusting for multiple comparisons using Hochberg<sup>1</sup> procedure.

† p-value not statistically significant at  $\alpha=0.05$  after adjusting for multiple comparisons using Hochberg<sup>1</sup> procedure.

Source: Tables 12.12, 12.13, 12.16, and 12.17 of Study 902 Clinical Report. Table 21 of Study 907 Clinical Report.

Table 9:

Proportion of Patients with Plasma HIV-1 RNA  $\leq 400$  copies/mL at Week 24  
 by Randomization Strata—Study 902 and 907 (ITT Population)

Randomization Strata / Subgroup	Study 902				Study 907			
	TDF 300 mg (n=54)	Placebo (n=28)	Treatment Effect (TDF-PLA)	p-value	TDF 300 mg (n=368)	Placebo (n=182)	Treatment Effect (TDF-PLA)	p-value
Plasma HIV-1 RNA Stratum								
<5,000 copies/mL	39% (11/28)	20% (2/10)	19%	0.276 †	52% (141/269)	17% (23/139)	35%	0.0000*
$\geq 5,000$ copies/mL	12% (3/26)	22% (4/18)	-10%	0.346 †	14% (14/99)	0% (0/43)	14%	0.0097*
CD4 Stratum								
<200 cells/mm <sup>3</sup>	13% (2/15)	0% (0/7)	13%	1.000 ‡	36% (16/45)	5% (1/21)	31%	0.0082*
$\geq 200$ cells/mm <sup>3</sup>	31% (12/39)	29% (6/21)	2%	0.861 †	43% (139/323)	14% (22/161)	29%	0.0000*
Prior ARV Drug Stratum								
<4 drugs	36% (5/14)	17% (1/6)	19%	0.613 †	60% (37/62)	15% (5/33)	45%	0.0000*
$\geq 4$ drugs	23% (9/40)	23% (5/22)	0%	1.000 ‡	39% (118/306)	12% (18/149)	27%	0.0000*

Note 1: Missing observations treated as failure for the proportions endpoints (i.e., %  $\leq 400$  or %  $\leq 50$ ).

Note 2: P-values compare TDF 300 mg vs. Placebo. P-value is based on Cochran Mantel-Haenszel test for general association unless specified otherwise.

\* p-value is statistically significant at  $\alpha=0.05$  after multiplicity adjustment using Hochberg<sup>1</sup> procedure.

† p-value not statistically significant at  $\alpha=0.05$  with multiplicity adjustment using Hochberg<sup>1</sup> procedure.

‡ p-value based on Fisher's exact test since chi-square test is not valid. Not statistically significant at  $\alpha=0.05$ .

Source: Tables 13.12 and 13.13 of Study 902 Clinical Report. FDA Analysis for CD4 and Prior ARV stratum for Study 902. Table 24.1 of Study 907 Clinical Report.

Table 10:

Proportion of Patients with Plasma HIV-1 RNA ≤50 copies/mL at Week 24  
 by Randomization Strata—Study 902 and 907 (ITT Population)

Randomization Strata / Subgroup	Study 902				Study 907			
	TDF 300 mg (n=54)	Placebo (n=28)	Treatment Effect (TDF-PLA)	p-value	TDF 300 mg (n=368)	Placebo (n=182)	Treatment Effect (TDF-PLA)	p-value
Plasma HIV-1 RNA Stratum								
<5,000 copies/mL	21% (6/28)	0% (0/10)	21%	0.115 †	26% (71/269)	1% (2/139)	25%	0.001*
≥5,000 copies/mL	4% (1/26)	17% (3/18)	-13%	0.150 †	5% (5/99)	0% (0/43)	5%	0.135 †
CD4 Stratum								
<200 cells/mm <sup>3</sup>	0% (0/15)	0% (0/7)	0%	1.000 ‡	27% (12/45)	0% (0/21)	27%	0.009*
≥200 cells/mm <sup>3</sup>	18% (7/39)	14% (3/21)	4%	1.000 ‡	20% (64/323)	1% (2/161)	19%	0.001*
Prior ARV Drug Stratum								
<4 drugs	29% (4/14)	0% (0/6)	29%	0.267 †	32% (20/62)	0% (0/33)	32%	0.001*
≥4 drugs	8% (3/40)	14% (3/22)	-6%	0.657 †	18% (56/306)	1% (2/149)	17%	0.001*

NA = P-value not calculated.

Note 1: Missing observations treated as failure for the proportions endpoints (i.e., % ≤400 or % ≤50).

Note 2: P-values compare TDF 300 mg vs. Placebo. P-value is based on Cochran Mantel-Haenszel test for general association.

\* p-value is statistically significant at  $\alpha=0.05$  with multiplicity adjustment using Hochberg<sup>1</sup> procedure.

† p-value not statistically significant at  $\alpha=0.05$  with multiplicity adjustment using Hochberg<sup>1</sup> procedure.

‡ p-value based on Fisher's exact test since chi-square test is not valid. Not statistically significant at  $\alpha=0.05$ .

Source: Tables 16.12, 16.13 of Study 902 Clinical Report. FDA Analysis for CD4 and Prior ARV stratum for Study 902. FDA Analysis for Study 907

## 5. Virology Substudy of Studies 902 and 907—Efficacy Analyses

The applicant also conducted a virology substudy (in order to perform genotypic and phenotypic analyses) for each of the two Studies 902 and 907. Efficacy analyses were performed for patients in these virology substudies. In this part of the review, results will be presented only for the Placebo arm and TDF 300 mg arm for both studies for the genotyping substudy.

Per the clinical virology protocols for Studies 902 and 907, HIV-1 RT and protease genes from banked plasma samples from the patients in the genotyping substudy were genotypically analyzed at Baseline and Week 24 (or upon early termination) by [REDACTED] (Study 907) or [REDACTED] (Study 902). Phenotypic analyses of susceptibility to Tenofovir DF and all approved nucleoside analogs were performed at Baseline and Week 24 (or upon early termination) for all patients in the phenotyping substudy using the Antivirogram™ recombinant virus assay.

These substudies consisted of a cohort of patients who were randomly assigned in the original study. In Study 907, approximately 50% (n=274) of the enrolled patients were included in the genotypic analyses substudy and 50% of these patients were included in the phenotypic analyses substudy (n=137). In the substudy 907, the randomization was balanced across all strata and maintained a 2:1 ratio of Tenofovir DF 300 mg versus Placebo. For Study 902, the virology substudy included all the originally randomized patients (ITT, n=186) for the genotypic analyses. In Study 902, phenotypic analyses were attempted for all patients treated with TDF 300 mg at study entry (n=54); successful phenotypic results were generated for 44 of these patients.

### a. Genotypic Analyses

The genotyping substudy for Virology Protocol 907 included 274 patients. Of these 21 patients were excluded from the virology ITT population (n=253) because these 21 patients failed to yield a sufficient PCR product at baseline for genotypic analysis. In the genotyping substudy for 902, baseline genotypic data was available for 184 out of 186 patients (n=26 in Placebo arm and n=54 in TDF 300 mg); plasma HIV from 2 patients, both in the placebo arm, failed to generate a sufficient PCR product for genotypic analysis.

#### Statistical Reviewer's Comments:

The reviewer pooled genotype data for both Studies 902 and 907 in order to examine the efficacy of TDF 300 mg as compared to Placebo because patients in both studies were treatment-experienced and the two studies were similar in design; in particular the randomization ratio of patients in Tenofovir DF 300 mg vs. Placebo was 2:1 in both studies. Hence pooling of data was considered appropriate.

Consistent with the extensive treatment experience of patients in both Studies 902 and 907, a summary of the baseline genotypic analysis (pooled for both Studies 902 and 907) showed that at Baseline, almost all of the patients expressed one or more primary

nucleoside-associated resistance mutations in reverse transcriptase (RT), more than half of them expressed primary protease-inhibitor (PI)-associated resistance mutations and about half of them expressed primary NNRTI-associated resistance mutations.

The applicant had pre-defined four genotypic subgroups of patients in the Clinical Virology Protocols for 902 and 907, in whom efficacy of Tenofovir DF was to be compared to the Placebo group. These four genotypic groups were as follows:

Group 1: No AZT-associated mutations, wild-type 184

Group 2: AZT-associated mutations, wild-type 184

Group 3: No AZT-associated mutations, M184V/I

Group 4: AZT-associated mutations, M184 V/I

The AZT-associated mutations were protocol-defined as one or more of the following substitutions in HVI RT: M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N. Mixtures of mutant and wild-type at any of these residues were to be grouped along with full mutants for the purpose of analyses. Note that AZT will also be referred to as ZDV (zidovudine).

Responses to the TDF therapy were compared between TDF 300 mg and the Placebo arm at Week 24 among patients in each of the four genotypic groups. These results are shown in Table 11.

Table 11:  
 HIV RNA Responses at Week 24 by Baseline Resistance Mutations in  
 Studies 902 and 907 combined (ITT Population)

Genotype Group	DAVG <sub>24</sub>	Tenofovir DF 300mg			Placebo			Net Viral Load Reduction (TDF-Placebo)	p-value (TDF vs. Placebo)
		n	Mean	(SD)	n	Mean	(SD)		
<b>Group 1</b> (No ZDV-R, Wild-type 184)		17	-0.32	(0.72)	9	-0.08	(0.48)	<b>-0.23</b>	0.321
<b>Group 2</b> (ZDV-R, Wild-type 184)		56	-0.45	(0.48)	31	0.13	(0.41)	<b>-0.58</b>	<0.001*
<b>Group 3</b> (No ZDV-R, M184V)		51	-0.96	(0.65)	20	-0.12	(0.39)	<b>-0.84</b>	<0.001*
<b>Group 4</b> (ZDV-R, M184V)		98	-0.52	(0.57)	50	-0.07	(0.52)	<b>-0.45</b>	<0.001*

Note 1: P-values are calculated based on a two-sample t-test for comparing TDF 300 mg versus Placebo.  
 Note 2: ZDV-R = ZDV-associated mutations which were protocol-defined as M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in Reverse Transcriptase (RT).  
 \* Statistically significant at 0.05 level of significance.

Source: FDA analyses

As shown in Table 11, the net reduction in viral load is statistically significant favoring Tenofovir DF 300 mg as compared to Placebo in Groups 2, 3, and 4 when either or both of AZT-associated mutations and M184V mutation were present at baseline. For Group 1 (No AZT-associated mutation and wild-type 184), the result was not statistically significant which may be due to the small number of patients in each treatment group who did not have AZT-associated mutation and had wild-type 184. The net mean reduction in viral load, however, was -0.23, which was numerically in favor of TDF 300 mg.

In addition, an exploratory analysis was done by the Statistical Reviewer to examine whether the presence or absence of AZT-associated mutations (predefined as M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N in Reverse Transcriptase), or the presence or absence of M184V mutation affected the treatment response to Tenofovir DF 300 mg relative to Placebo. This is the same as a statistical test for interaction between the treatment groups (TDF and Placebo) and the mutation Groups 1, 2, 3 and 4 mentioned earlier. The corresponding results are shown in Table 12.

Table 12:

HIV RNA Responses at Week 24  
 by Presence or Absence of ZDV-associated mutations or M184V mutation at Baseline  
 in Studies 902 and 907 combined (ITT Population)

Baseline Genotype Group	Tenofovir DF 300mg			Placebo			Net Viral Load Reduction (TDF-Placebo)	p-value (No ZDV-R vs ZDV-R or Wild-type 184 vs M184V)
	DAVG <sub>24</sub>			DAVG <sub>24</sub>				
	n	Mean	(SD)	n	Mean	(SD)		
No ZDV-R	68	-0.80	(0.72)	29	-0.11	(0.41)	<b>-0.69</b>	0.889 †
ZDV-R	154	-0.50	(0.54)	81	+0.00	(0.49)	<b>-0.50</b>	
Wild-type 184	73	-0.42	(0.54)	40	+0.08	(0.43)	<b>-0.50</b>	0.131*
M184V	149	-0.67	(0.63)	70	-0.08	(0.49)	<b>-0.59</b>	
Test for 3 <sup>rd</sup> order interaction effect between Treatment, ZDV-R, and M184V								0.005*
Note 1: P-values are calculated based on an ANOVA model that included main effects for treatment group, presence or absence of ZDV-R, presence or absence of M184V; second order interactions for treatment by ZDV-R, treatment by M184V, and third order interaction between treatment by ZDV-R by M184V. Note 2: ZDV-R = ZDV-associated mutations which were protocol-defined as M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N in Reverse Transcriptase (RT). * Statistically significant at 0.15 level of significance for a test of interaction effect.								

Source: FDA analyses

As shown in Table 12, there was highly statistically significant (p-value=0.005) third order interaction effect between the treatment groups, presence or absence of ZDV-associated mutations, and presence or absence of M184V mutation.

The interpretation of this third-order interaction effect is that ZDV-associated mutations and/or M184V can work antagonistically or synergistically on the treatment effect due to Tenofovir DF 300 mg. In other words, the interpretation is as follows:

Given that either

- a) when M184V mutation is present, the treatment effect of Tenofovir DF 300 mg relative to Placebo can vary in the presence or absence of ZDV-associated mutations, and/or
- b) when ZDV-associated mutations are present, the treatment effect of Tenofovir DF 300 mg relative to Placebo can vary in the presence or absence of M184V (M184V absent implies presence of Wild-type 184).

To evaluate the above interpretation, see Table 11, which shows that when M184V mutation is present at baseline, the net viral load reduction at Week 24 due to Tenofovir is  $-0.84 \log_{10}$  copies/mL in the absence of ZDV-associated mutations (Group 3), which is higher as compared to a net reduction of  $-0.45 \log_{10}$  copies/mL in the presence of ZDV-associated mutations (Group 4). However, when wild-type 184 mutation is present there is not enough evidence whether presence or absence of ZDV-associated mutations significantly affects the response (Treatment effect for Group 2 of  $-0.58 \log_{10}$  copies/mL vs treatment effect for Group 1 of  $-0.23 \log_{10}$  copies/mL is not statistically significant).

Similarly, in the absence of ZDV-associated mutations at baseline, patients with the M184V mutation (Group 3) had a higher net reduction in viral load of  $-0.84 \log_{10}$  copies/mL than those who had wild-type 184 (Group 1 had  $-0.23 \log_{10}$  copies/mL reduction in viral load). However, in the presence of ZDV-associated mutations (Group 2 vs Group 4), the M184V mutation did not significantly change the net viral load response to TDF 300 mg.

In summary, the presence of M184V mutation generated the highest response in terms of viral load reduction due to Tenofovir DF 300mg when AZT-associated mutations were absent. This gives preliminary evidence that the M184V mutation may work synergistically with Tenofovir DF. On the other hand, the presence of AZT-associated mutations tended to reduce the response due Tenofovir DF 300 mg. A caveat to this statistical analysis is that the resistance pattern which would account for other mutation patterns of the HIV-1 in treatment-experienced patients has not been taken into consideration.

## **D. Statistical Reviewer's Analyses**

### **1. Plasma HIV-1 RNA**

The Statistical Reviewer conducted additional sensitivity analyses on the primary efficacy variable of the time-weighted change from baseline in HIV RNA at Weeks 4, 24 and 48 (DAVG<sub>xx</sub>) for Studies 902 and 907 in order to examine the robustness of the primary efficacy results. The scenarios considered were as follows:

- DAVG carried forward

In the *DAVG carried forward* scenario, if a patient does not have data beyond visit  $x$ , then the DAVG for visits beyond time point  $x$  are same as DAVG <sub>$x$</sub> . For example, if a patient is lost-to-follow at Week 8, then DAVG<sub>24</sub> for Week 24 is equal to the DAVG<sub>8</sub> at Week 8.

- Baseline carried forward

In the *Baseline carried forward* scenario, if a patient does not have data beyond visit  $x$ , then it is assumed that viral load of the patient beyond that time point returns to the baseline viral load, and all DAVG beyond visit  $x$  are assumed to be equal to the baseline value.

The scenario used by the Applicant was the *DAVG carried forward*. The other scenario, *Baseline carried forward* is a more conservative scenario because in this scenario it is assumed that if a patient does not have data beyond a certain visit, say  $x$ , then the patient has stopped therapy at visit  $x$ , after which, their viral load will not remain/continue to get suppressed. Instead is more likely that after visit  $x$ , the viral load of the patient will rebound to the original baseline value. In addition, the *baseline carried forward* scenario more appropriately assesses the efficacy of the drug if a study has several drop-outs.

Results from these two scenarios are shown in Table 13 and Table 14 for Study 902, and Table 16 and Table 17 for Study 907.

In addition to the *DAVG carried forward* scenario and *Baseline carried forward* scenario, a third scenario for sensitivity analyses is to use the *Baseline carried forward scenario* while taking into account patients who added or changed any background therapy and treating these patients as failures. At the time point that a patient changes/switches therapy, it is assumed that the viral load returns to the baseline value from that point forward.

In Study 902 and 907, since the number of patients who added/changed background therapy was relatively small and the efficacy results for the DAVG<sub>24</sub> endpoint were robust for the *Baseline carried forward scenario*, it was expected that the third scenario for

sensitivity analyses would provide similar primary efficacy results. This discussion is made later with respect to the secondary endpoint of proportions.

**b. Study 902**

Table 13:

Time-Weighted Change from Baseline (DAVG<sub>xx</sub>) in log<sub>10</sub> HIV-1 RNA Levels  
 by Treatment Group—Study 902 (ITT Population)  
 (Scenario: FDA Analysis—DAVG Carried Forward)

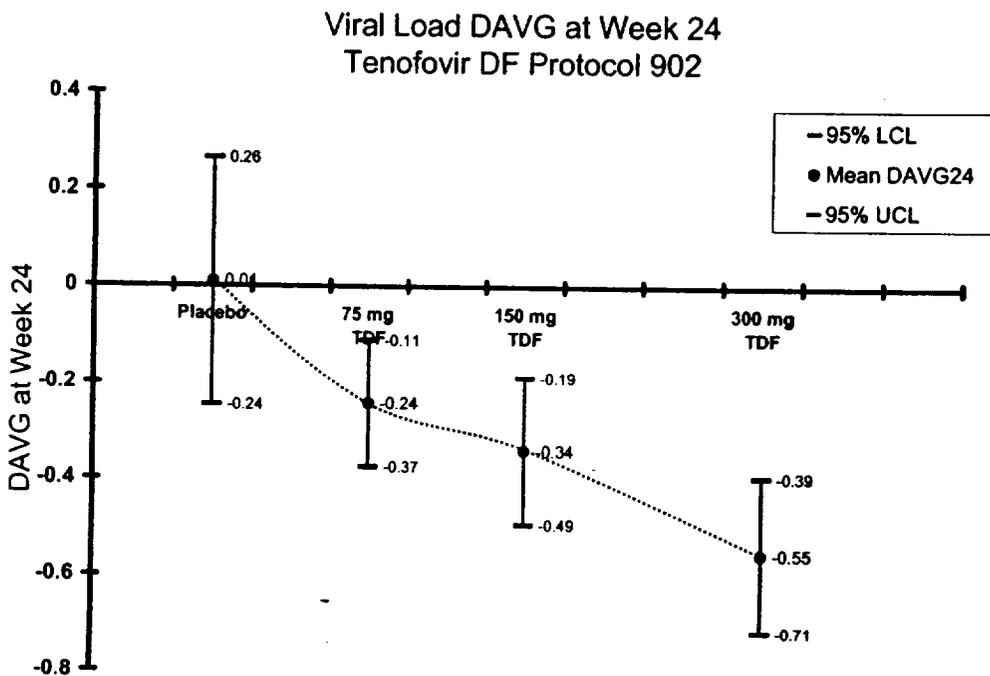
Timepoint	Placebo	Tenofovir DF			Placebo cross-over to TDF 300 mg (24-48 weeks)
		75 mg	150 mg	300 mg	
<b>Week 4</b>					
n	28	53	50	54	—
Mean (Std. Dev.)	0.02 (0.32)	-0.18 (0.27)	-0.35 (0.33)	-0.50 (0.41)	—
Median	-0.00	-0.12	-0.31	-0.46	—
p-value		0.005*	<0.001*	<0.001*	
<b>Week 24</b>					
n	27	53	51	54	1
Mean (Std. Dev.)	0.009 (0.67)	-0.24 (0.49)	-0.34 (0.55)	-0.55 (0.60)	0.42 (NA)
Median	0.02	-0.13	-0.24	-0.52	0.42
p-value		0.099 †	0.0236*	<0.001*	
<b>Week 48</b>					
n	7	53	51	54	21
Mean (Std. Dev.)	0.28 (0.31)	-0.31 (0.56)	-0.34 (0.56)	-0.59 (0.61)	-0.33 (0.70)
Median	0.29	-0.29	-0.29	-0.56	-0.32
P-values calculated are based on a two-sample t-test for pairwise comparisons between TDF and Placebo. Note: P-values were not calculated for Week 48 because patients randomized to placebo crossed-over to TDF 300 mg at Week 24. * P-value is statistically significant after multiplicity adjustment using Holm's procedure for overall level of significance of 0.05. † Not statistically significant at $\alpha = 0.05$ .					

Source: FDA Analysis.

Although the scenario, *DAVG carried forward*, was the same for the FDA Reviewer's analysis shown in Table 13 and the Applicant's results shown in Table 4, the results for DAVG did not match identically. The reason for the difference was the methodology used by the Applicant in computing the DAVG variable. For a given patient, the DAVG at, say Week 24, i.e., DAVG<sub>24</sub> is the Area Under the Curve (AUC) of the measurement through Week 24 minus the Baseline value.

The applicant computed the Area Under the Curve (AUC) for the viral load for, say Week

24, starting at the time point of the first post-baseline visit, i.e., Week 2. In comparison, the preferred method is to calculate the AUC starting from Week 0 (baseline) through Week 24, because the patient is randomized to treatment at Week 0. Therefore any change in viral load that happens between Week 0 and Week 2 is also captured. The FDA Reviewer used the second methodology resulting in the numbers shown in Table 13. As a result the primary efficacy results obtained by the FDA Reviewer showed numbers that were slightly smaller in magnitude. For example, the Week 24 DAVG for TDF 300 mg was  $-0.55 \log_{10}$  using the Reviewer's analysis (see Table 10) as compared to  $-0.58 \log_{10}$  using the Applicant's analysis (see Table 4). Since the difference in these numbers were small, the rest of Statistical Review will use the Applicant's numbers.



Source: FDA Analysis shown in Table 13

Figure 2: Time-Weighted Average Change from Baseline at Week 24 (DAVG<sub>24</sub>) in  $\log_{10}$  HIV-1 RNA Levels—Study 902

As shown in Table 13 and Figure 2, there was a greater reduction in viral load due to Tenofovir DF as compared to placebo at Week 24 as the dose increased from 75 mg to 150 mg to 300 mg (DAVG<sub>24</sub> = 0.01 for Placebo, and  $-0.24$ ,  $-0.34$ ,  $-0.55$ , for TDF 75 mg, 150 mg, and 300 mg respectively).

Also the net treatment effect (net mean reduction in viral load) due to Tenofovir DF 300 mg as compared to placebo was  $-0.56 \log_{10}$  and was statistically significant at  $\alpha = 0.05$ .

Table 14:

Time-Weighted Change from Baseline (DAVG<sub>xx</sub>) in  $\log_{10}$  HIV-1 RNA Levels  
 by Treatment Group—Study 902 (ITT Population)  
 (Scenario: FDA Analysis—Baseline Carried Forward)

Timepoint	Placebo	Tenofovir DF			Placebo cross-over to TDF 300 mg (24-48 weeks)
		75 mg	150 mg	300 mg	
<b>Week 4</b>					
n	28	53	50	54	—
Mean (Std. Dev.)	0.02 (0.31)	-0.18 (0.27)	-0.35 (0.33)	-0.50 (0.40)	—
Median	-0.00	-0.12	-0.28	-0.42	—
p-value		0.004*	<0.001*	<0.001*	
<b>Week 24</b>					
n	27	53	51	54	1
Mean (Std. Dev.)	-0.01 (0.67)	-0.24 (0.49)	-0.34 (0.54)	-0.54 (0.60)	0.42 (NA)
Median	0.04	-0.13	-0.24	-0.49	0.42
p-value		0.114†	0.027†	<0.001*	
<b>Week 48</b>					
n	7	53	51	54	21
Mean (Std. Dev.)	0.18 (0.31)	-0.30 (0.53)	-0.36 (0.50)	-0.56 (0.59)	-0.33 (0.69)
Median	0.06	-0.28	-0.26	-0.53	-0.32
P-values calculated are based on a two-sample t-test for pairwise comparisons between TDF and Placebo. Note: P-values were not calculated for Week 48 because patients randomized to placebo crossed-over to TDF 300 mg at Week 24. * P-value is statistically significant after multiplicity adjustment using Holm's multiplicity adjustment procedure for overall level of significance of 0.05. † Not statistically significant after multiplicity adjustment.					

Source: FDA Analysis.

Recall that Study 902 was carried out for 48 weeks. Majority of the patients in this study completed 48 weeks of treatment and there were very few dropouts. Due to this, the analysis based on the scenario, *Baseline carried forward*, showed similar results as the previous scenario which indicated the robustness of the primary efficacy results.

There appeared to be a dose-related response to Tenofovir DF treatment as the dose increased from 75 mg to 300 mg (see Table 14). Also, the primary efficacy of the chosen dose TDF 300 mg was established by showing a net reduction in viral load of  $-0.53 \log_{10}$  (TDF 300mg -Placebo =  $-0.54 - (-0.01) = -0.53$ ) which was statistically significant (p-

value<0.001) at  $\alpha=0.05$  overall level of significance. The Tenofovir DF 75 mg group was not statistically significantly different from Placebo, while Tenofovir DF 150 mg dose showed only marginal significance when compared to Placebo (p-value=0.027 compared to  $\alpha/2=0.025$  after adjusting for multiplicity).

Table 15:

Proportion of Patients with HIV-1 RNA  $\leq 400$  copies/mL or  $\leq 50$  copies/mL  
 at Week 24—Study 902 (ITT Population)  
 (Scenario: Missing = Failures;  
 Addition/Change in background ARV therapy treated as failures)

Study		Treatment Group			
		Placebo	Tenofovir DF		
Success criteria			75 mg	150 mg	300 mg
902	$\leq 400$ copies/ml	2/28 (7%)	5/53 (9%)	6/51 (12%)	10/54 (19%)
	p-value for dose-response trend	0.097 <sup>a</sup>			
	$\leq 50$ copies/ml	0/28 (0%)	2/53 (4%)	1/51 (2%)	6/54 (11%)
	p-value for dose-response trend	0.032 <sup>*</sup>			

NOTE 1: Ultrasensitive assay was used for both studies.  
 NOTE 2: The applicant considered the patients with viral load equal to 400 copies/mL or equal to 50 copies/mL as successes. These are typically evaluated (in other HIV clinical trials) as failures.  
<sup>a</sup> P-value based on Cochran-Mantel-Haenszel test of correlation between treatment groups and success criteria. Not statistically significant at 0.05 level.  
<sup>\*</sup> P-value based on exact Mantel-Haenszel test of correlation between treatment groups and success criteria. Exact test used since 50% of the expected cell counts were less than 5. Statistically significant at 0.05 level.

Source: FDA Analysis.

In an earlier table, Table 5, the Applicant's results for the second efficacy endpoint of *proportion below pre-specified levels at Week 24* in the ITT population were shown. Those results were based on treating missing values as failures. However, in that intent-to-treat analysis, the Applicant had not treated patients who added a drug or changed the background therapy as failures. The Statistical Reviewer considered these patients as failures and recomputed the proportion of patients who achieved viral load  $\leq 400$  copies/mL or  $\leq 50$  copies/mL. Note that the Ultrasensitive assay was used to measure viral load.

As shown in Table 15, 7% (2/28) of the patients in the Placebo group achieved  $\leq 400$  copies/mL at Week 24 and had not added or changed the background therapy, as compared to 19% (10/54) in the Tenofovir DF 300 mg group. The difference in response between TDF 300 mg and Placebo, i.e., the treatment effect, was 12% with a 95% confidence interval of (-10%, 31%). However, this difference was not statistically significant because the test for a dose-response trend showed a p-value of 0.097.

The proportions of patients who achieved  $\leq 50$  copies/mL at Week 24 was 0% (0/28) in the Placebo group versus 11% (6/54) in the Tenofovir DF 300 mg. A statistical test for a dose-response was also performed for this endpoint which showed a statistical significance with p-value of 0.032. The difference in response between TDF 300 mg and Placebo, with respect to  $\% \leq 50$  copies/mL was 11% with a 95% confidence interval of (-8%, 27%).

c. **Study 907**

Similarly, for Study 907, the Reviewer conducted primary efficacy analyses for the two scenarios: *DAVG carried forward* and *Baseline carried forward* which are shown in Table 16 and Table 17, respectively.

The primary efficacy results for Study 907 for the first scenario shown in Table 16 are consistent with the Applicant's results shown in Table 4.

Table 16:

Time-Weighted Change from Baseline (DAVG<sub>xx</sub>) in log<sub>10</sub> HIV-1 RNA Levels  
 by Treatment Group—Study 907 (ITT Population)  
 (Scenario: FDA Analysis—DAVG Carried Forward)

Timepoint	Placebo	Tenofovir DF 300 mg	Net Treatment Effect (TDF-Placebo)	p-value
<b>Week 4</b>				
n	182	366		
Mean (Std. Dev.)	-0.02 (0.26)	-0.43 (0.40)	-0.41	<0.001*
Median	-0.00	-0.39	-0.39	
<b>Week 24</b>				
n	182	367		
Mean (Std. Dev.)	-0.03 (0.33)	-0.58 (0.57)	-0.55	<0.001*
Median	-0.02	-0.54	-0.52	
<b>Week 48</b>				
n	182	367		
Mean (Std. Dev.)	-0.09 (0.37)	-0.58 (0.57)	-0.49	
Median	-0.10	-0.55	-0.45	
P-values calculated are based on a two-sample t-test.				
Note: Patients randomized to Placebo crossed-over to TDF 300 mg at Week 24.				
* P-value statistically significant at 0.05 level of significance.				

Source: FDA Analysis.

In Study 907, the net mean reduction in viral load at Week 24 due to Tenofovir DF 300 mg as compared to Placebo was  $-0.55 \log_{10}$  and was statistically significant. The comparison between TDF 300 mg for Week 48 is not very meaningful because

patients randomized to Placebo crossed-over to TDF 300 mg after Week 24.

Table 17:

Time-Weighted Change from Baseline (DAVG<sub>xx</sub>) in log<sub>10</sub> HIV-1 RNA Levels  
 by Treatment Group—Study 907 (ITT Population)  
 (Scenario: FDA Analysis—Baseline Carried Forward)

Timepoint	Placebo	Tenofovir DF 300 mg	Net Treatment Effect (TDF-Placebo)	p-value
<b>Week 4</b>				
n	182	366		
Mean (Std. Dev.)	-0.02 (0.26)	-0.43 (0.40)	-0.41	<0.001*
Median	-0.00	-0.39	-0.39	
<b>Week 24</b>				
n	182	367		
Mean (Std. Dev.)	-0.03 (0.33)	-0.57 (0.57)	-0.54	<0.001*
Median	-0.02	-0.52	-0.50	
<b>Week 48</b>				
n	182	367		
Mean (Std. Dev.)	-0.09 (0.29)	-0.39 (0.43)	-0.30	<0.001
Median	-0.07	-0.35	-0.28	
P-values calculated are based on a two-sample t-test.				
Note: Patients randomized to Placebo crossed-over to TDF 300 mg at Week 24.				
* P-value statistically significant at 0.05 level of significance.				

Source: FDA Analysis.

The analysis based on the baseline-carried-forward scenario also showed similar results at Week 24. The net mean reduction in viral load at Week 24 due to Tenofovir DF 300 mg was  $-0.54 \log_{10}$ . However, after Week 24, the number of patients followed through Week 48 reduced because several patients either rolled-over to Protocol 910 (roll-over study) or dropped-out of the study. Due to this reason, the baseline-carried-forward scenario shows conservative results for Week 48 and shows a lower reduction in viral load due to Tenofovir DF.

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Table 18:

Proportion of Patients with HIV-1 RNA  $\leq 400$  copies/mL or  $\leq 50$  copies/mL  
 at Week 24—Study 907 (ITT Population)  
 (Scenario: Missing = Failures;  
 Addition/Change in background ARV therapy treated as failures)

Success Criteria	Treatment Group	
	Placebo	Tenofovir DF 300 mg
$\leq 400$ copies/ml	20/182 (11%)	149/368 (40%)
Treatment Effect (95% CI)	29% (22%, 37%)	
p-value	0.001*	

$\leq 50$ copies/ml	2/182 (1%)	72/368 (20%)
Treatment Effect (95% CI)	19% (13%, 24%)	
p-value	0.001*	

NOTE 1: Ultrasensitive assay was used for both studies.  
 NOTE 2: The applicant considered the patients with viral load equal to 400 copies/mL or equal to 50 copies/mL as successes. These are typically evaluated (in other HIV clinical trials) as failures.  
 p-value is based on the Cochran Mantel-Haenszel test for general association.  
 \* Statistically significant for both success criteria (i.e.,  $\leq 400$  copies/mL and  $\leq 50$  copies/mL) at two-sided  $\alpha = 0.05$

Source: FDA Analysis.

Secondary efficacy analyses were also conducted for Study 907 based on the proportions endpoint. As discussed for Study 902, the Statistical Reviewer re-calculated the proportion of patients who achieved viral load  $\leq 400$  copies/mL or  $\leq 50$  copies/mL at Week 24 by treating patients who added a new drug or changed background therapy as failures.

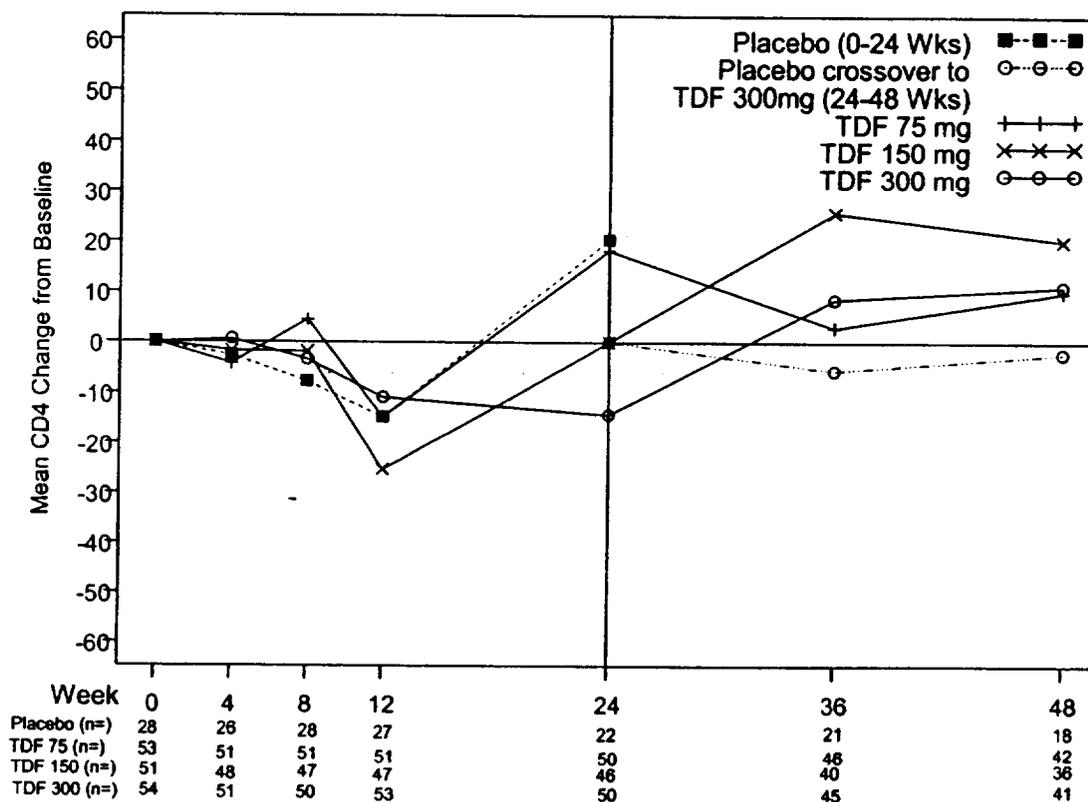
These results are shown in Table 18. Both of the proportions endpoints showed a statistically significant result favoring Tenofovir DF 300 mg against Placebo. The net proportion of patients achieving viral load  $\leq 400$  copies/mL or  $\leq 50$  copies/mL at Week 24 due to TDF 300 mg was 29% (95% CI: [22%, 37%]) or 19% (95% CI: [13%, 24%]), respectively.

## 2. CD4+ Cell Count

Figure 3 and Figure 4 below show plots of the mean change from baseline in CD4+ cell counts in Studies 902 and 907.

As discussed earlier and shown in Table 6 and Figure 3 (below), in Study 902, there was no consistent pattern of either increase or decrease in CD4+ cell counts through Week 48 in either the Placebo arm or any of the three Tenofovir DF (75mg, 150mg, or 300mg) groups. Note that at best, the mean increase in CD4+ cell count from baseline in any group was about 20 cells/mm<sup>3</sup> which is a modest increase when compared to the variability (standard deviation) in CD4+ cell counts of about 200 cells/mm<sup>3</sup> between patients.

Mean Change in CD4+ Cell Count from Baseline, Protocol 902



Source: FDA analysis and Tables 28 and 28.2 of 907 Clinical Study Report.

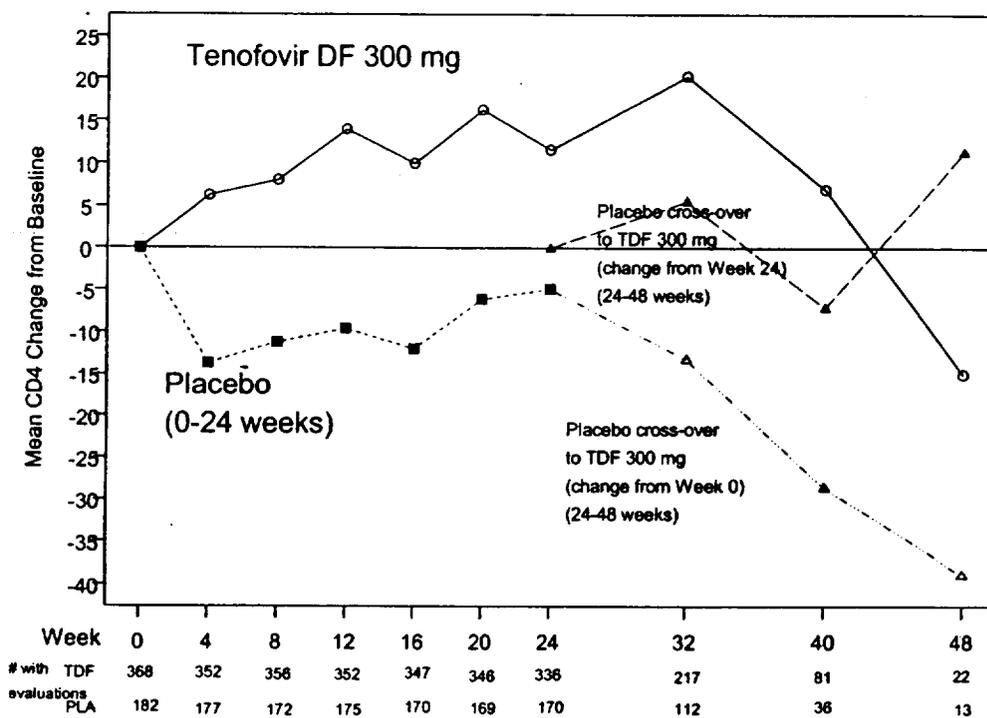
Figure 3: Mean Change from Baseline in CD4+ Cell Count through Week 48—Study 902

In the larger study, Study 907, patients in the Tenofovir DF 300 mg group had a mean increase from baseline in CD4+ cells at Week 24 of approximately +12 cells/mm<sup>3</sup> while the patients in the Placebo group had a decrease from baseline of approximately -5 cells/mm<sup>3</sup>.

Through Week 32, the overall trend showed a modest and consistent increase in CD4+ cell count in favor of TDF 300 mg (see Figure 4). The time-weighted average change from baseline at Week 24, namely, DAVG24 (+13 cells/mm<sup>3</sup> for the TDF 300 mg versus -11 cells/mm<sup>3</sup> for the Placebo group) was in favor of Tenofovir DF 300 mg (see Table 7).

From Week 24 through Week 48, the number of patients that were followed declined which makes it difficult to interpret the long-term effect of Tenofovir DF on the CD4+ cell count. At Week 32, CD4+ cell count data was available for 112 patients who crossed-over from Placebo to TDF 300 mg after Week 24. The placebo cross-over patients did not show any conclusive pattern of change from Week 24 in CD4+ cell count. However, it appeared as though the mean change in CD4+ cell count when compared to Week 0 had declined.

Mean Change in CD4+ Cell Count from Baseline, Protocol 907



Source: FDA analysis and Tables 28 and 28.2 of 907 Clinical Study Report.

Figure 4: Mean Change from Baseline in CD4+ Cell Count through Week 48—Study 907

### 3. Subgroup Analyses

#### a. Randomization Strata

The FDA statistical reviewer performed subgroup analyses on the randomization strata to test for interaction effects between the treatment groups and randomization strata. These statistical tests would indicate whether the net treatment benefit (viral load reduction at Week 24) due to Tenofovir DF 300 mg as compared to Placebo differs significantly in one subgroup of patients versus another.

For Study 902, the randomization was stratified by baseline viral load (<20,000 or ≥20,000 copies/mL), baseline CD4 cell count (<200 or ≥200 cells/mm<sup>3</sup>) and the prior use of antiretroviral (ARV) drugs (<4 or ≥4 drugs).

In addition to the randomization strata, responses for the subgroup of patients with baseline viral load <5,000 copies/mL and ≥5,000 copies/mL were also examined for Study 902. These subgroups of patients were of interest because the median baseline viral load of patients in Study 902 was approximately 5000 copies/mL. In addition, this cut off of baseline viral load of 5000 copies/mL was used as the randomization strata in the larger Phase 3 study—Study 907.

For Study 907, the randomization was stratified by baseline viral load (<5,000 or ≥5,000 copies/mL), baseline CD4 cell count (<200 or ≥200 cells/mm<sup>3</sup>) and the prior use of antiretroviral (ARV) drugs (<4 or ≥4 drugs).

Table 19 shows responses (net viral load reduction) due to Tenofovir DF 300 mg as compared to Placebo in the subgroups of patients with baseline viral load either <5,000 copies/mL or ≥5,000 copies/mL; either <20,000 copies/mL or ≥20,000 copies/mL; baseline CD4 cell count either <200 cells/mm<sup>3</sup> or ≥200 cells/mm<sup>3</sup>; and prior antiretroviral drugs used either <4 drugs or ≥4 drugs.

Similarly, Table 20 shows responses (net viral load reduction) due to Tenofovir DF 300 mg as compared to Placebo in the subgroups of patients with baseline viral load either <5,000 copies/mL or ≥5,000 copies/mL; baseline CD4 cell count either <200 cells/mm<sup>3</sup> or ≥200 cells/mm<sup>3</sup>; and prior antiretroviral drugs used either <4 drugs or ≥4 drugs.

Statistical analyses testing for treatment by subgroup interaction were based on an ANOVA (analysis of variance) model that included main effects for treatment group and strata (subgroup) as well as interaction effects for treatment by stratum (subgroup).

Table 19:  
 Subgroup Analyses—Viral Load by Subgroup Interaction for  
 Study 902 (ITT Population)

Subgroup\ DAVG <sub>24</sub>	Tenofovir DF 300mg			Placebo			Net Viral Load Reduction (TDF-Placebo)	p-value (Treatment by Stratum interaction)
	n	Mean	(SD)	n	Mean	(SD)		
Plasma HIV-1 RNA <5,000 copies/mL	28	-0.68	(0.54)	10	0.33	(0.53)	-1.01	0.061*
≥5,000 copies/mL	26	-0.47	(0.70)	18	-0.16	(0.72)	-0.31	
Plasma HIV-1 RNA <20,000 copies/mL	47	-0.60	(0.66)	22	-0.05	(0.70)	-0.55	0.482
≥20,000 copies/mL	7	-0.32	(0.32)	6	0.24	(0.67)	-0.64	
CD4 stratum <200 cells/mm <sup>3</sup>	15	-0.24	(0.42)	7	0.33	(0.31)	-0.57	0.187
≥200 cells/mm <sup>3</sup>	39	-0.71	(0.65)	21	-0.09	(0.76)	-0.62	
Prior ARV drug use <4 drugs	33	-0.59	(0.61)	17	-0.24	(0.69)	-0.35	0.384
≥4 drugs	21	-0.56	(0.67)	11	0.41	(0.49)	-0.97	

Note: P-values are calculated based on an ANOVA (Analysis of Variance) model which included main effects for treatment group, randomization strata (or subgroup of interest in case of baseline viral load < or ≥ 5000 copies/mL), and treatment by stratum interaction.

\* p-value for treatment by subgroup interaction is statistically significant at  $\alpha=0.15$  level of significance. This indicates that the net treatment effect of tenofovir DF 300 mg is larger in one subgroup of patients vs. another.

Source: Tables 12.12, 12.13, 12.16 and 12.17 of 902 Clinical Study Report. FDA analyses on treatment by stratum interaction.

As shown in Table 16, the net treatment effect (reduction in viral load at Week 24) due to Tenofovir DF 300 mg in patients with baseline viral load <5,000 copies/mL was significantly higher (-1.01 log<sub>10</sub>) as compared to that for patients with baseline viral load ≥5,000 copies/mL (-0.31 log<sub>10</sub>). The p-value of 0.061 for this test was statistically significant at a 0.15 level of significance which is typical for testing an interaction effect (The significance level,  $\alpha$ , for testing interaction effects could range from 0.1 to 0.2 depending on the sample size).

No statistically significant difference in the net viral load reduction due to Tenofovir DF 300 mg was observed between patients who had either <20,000 or ≥20,000 copies/mL viral load at baseline. Note that in Study 902 the number of patients with baseline viral load ≥20,000 copies/mL was much smaller (7 patients in TDF 300mg group and 6 patients in Placebo group).

The other subgroups of patients with baseline CD4 cell counts either <200 or ≥200 cells/mm<sup>3</sup> or the subgroup of patients who used either <4 or ≥4 ARV drugs previously, did not show statistically significant differences in net treatment effects due to Tenofovir DF 300 mg. However, note that Study 902 is a Phase 2 study with small number of patients in each subgroup and is not statistically powered to detect

numerically small differences in treatment by subgroup interaction effects unless the differences are much larger.

Similar analyses were performed for the larger Phase 3 study—Study 907—with a total of 550 patients in the ITT population.

Table 20:  
 Subgroup Analyses—Viral Load by Randomization Strata Interaction for  
 Study 907 (ITT Population)

Stratum\ DAVG <sub>24</sub>	Tenofovir DF 300mg			Placebo			Net Viral Load Reduction (TDF-Placebo)	p-value (Treatment by Stratum interaction)
	n	Mean	(SD)	n	Mean	(SD)		
Plasma HIV-1 RNA								
<5,000 copies/mL	268	-0.59	(0.61)	139	+0.03	(0.33)	-0.62	0.206
≥5,000 copies/mL	99	-0.67	(0.61)	43	-0.22	(0.38)	-0.45	
CD4 stratum								
<200 cells/mm <sup>3</sup>	45	-0.39	(0.55)	21	+0.05	(0.37)	-0.44	0.230
≥200 cells/mm <sup>3</sup>	322	-0.64	(0.61)	161	-0.04	(0.35)	-0.60	
Prior ARV drug use								
<4 drugs	62	-0.89	(0.54)	33	-0.09	(0.33)	-0.80	0.045*
≥4 drugs	305	-0.56	(0.61)	149	-0.02	(0.36)	-0.54	

Note: P-values are calculated based on an ANOVA (Analysis of Variance) model which included main effects for treatment group, randomization strata, and treatment by stratum interaction.

\* p-value for treatment by stratum interaction is statistically significant at  $\alpha=0.15$  level of significance. This indicates that the net treatment effect of tenofovir DF 300 mg is larger in one subgroup of patients vs. another.

Source: Table 21 of 907 Clinical Study Report. FDA analyses on treatment by stratum interaction.

As shown in Table 20, the net treatment effect (reduction in viral load at Week 24) due to Tenofovir DF 300 mg in patients who previously used <4 antiretroviral drugs was significantly higher ( $-0.80 \log_{10}$ ) as compared to that for patients who were more treatment-experienced and had previously used  $\geq 4$  drugs ( $-0.54 \log_{10}$ ). The p-value of 0.045 for this test was statistically significant at a 0.15 level of significance, which is typical for testing an interaction effect ( $\alpha$  could range from 0.1 to 0.2 depending on the sample size).

For the other subgroups of patients, there was no statistically significant difference in the net treatment effect due to Tenofovir DF 300 mg for one subgroup of patients versus another after adjusting for other strata and treatment by stratum interaction. For example, the net reduction in viral load due to TDF 300 mg in patients with baseline viral load <5,000 copies/mL was  $-0.62 \log_{10}$  versus  $-0.45 \log_{10}$  in patients with baseline viral load  $\geq 5,000$  copies/mL. However, the net reduction in viral load at Week 24 was numerically higher in the “healthier” patients with baseline viral load <5,000 copies/mL and baseline CD4 cell count  $\geq 200$  cells/mm<sup>3</sup>. These results were consistent with those observed in the Phase 2 study, Study 902 (see Table 19). A

larger clinical trial would confirm whether these interaction effects are more likely to be true.

#### 4. Assessment of Bone Fractures

Since bone abnormalities were observed in non-clinical studies in animals receiving tenofovir (not tenofovir DF), occurrence of bone abnormalities were of concern in the clinical studies 902 and 907. A total of 15 patients who received any Tenofovir DF (75 mg, 150 mg, and 300 mg) in Studies 902 and 907, experienced bone fractures between 0 to 144 Weeks, as compared to 3 patients who received Placebo for 0-24 Weeks. As of August 15, 2001, follow-up data was available on patients in the Placebo arm (n=210) who were followed for 56 weeks and in all the Tenofovir DF arms (n=717) who were followed for approximately 2 ½ years (144 weeks).

Various approaches were taken by the Statistical Reviewer to evaluate the risk of bone fractures for patients receiving Tenofovir DF. Note that a direct comparison between patients receiving Tenofovir DF and patients receiving Placebo was available only for 0-24 weeks. After Week 24, comparative data was not available for Tenofovir DF, which makes the assessment of the incidence of bone fractures difficult. The following methods were used to assess the long-term risk of bone fractures:

- A Poisson regression was conducted to examine whether bone fracture rates varied over six-month intervals.
- A Kaplan-Meier curve estimating the incidence of bone fracture was created.
- The estimated cumulative hazard (i.e.,  $-\log(\text{survival})$ ) function over time was also created which would help assess whether the hazard of bone fractures changed over time.

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Table 21 below summarizes the incidence as well as rate of bone fractures over six-month intervals for all available data in Studies 902 and 907 through two years. As noted before, comparison of bone fracture rates in the Tenofovir DF arm and the Placebo can be made only for the first 24 weeks (~6 months). The bone fracture calculated based on person-years showed a rate of 1.7% in the TDF arms as compared to 3.2% in the Placebo arm. These rates were similar. Beyond six month time interval, data was sparse in the Placebo group. Therefore, the Statistical Reviewer examined to see if the rates of bone fracture had changed over time within the Tenofovir DF group using a Poisson regression model based on the logarithm of bone fracture rates.

As shown in Table 21, the odds ratio for a given six-month interval, say >12-18 months, compares the odds of the incidence of bone fractures as compared to the bone fracture rate at 0-6 months. The comparison of each six-month interval is made to the 0-6 month time interval. The odds ratio for the >12-18 month interval was 2.9 as compared to the 0-6 months, indicating that the incidence of bone fracture in >12-18 month is ~3 times more than that in 0-6 month. The 95% confidence interval of the odds ratio for the >12-18 month time interval was (0.9, 9.5) and was marginally significant (p-value=0.078). This may indicate an increase in bone fracture rates in Tenofovir DF group between 1 year to 1 ½ years. However, the evidence is not conclusive. None of the other odds ratios were statistically significant.

Table 21:

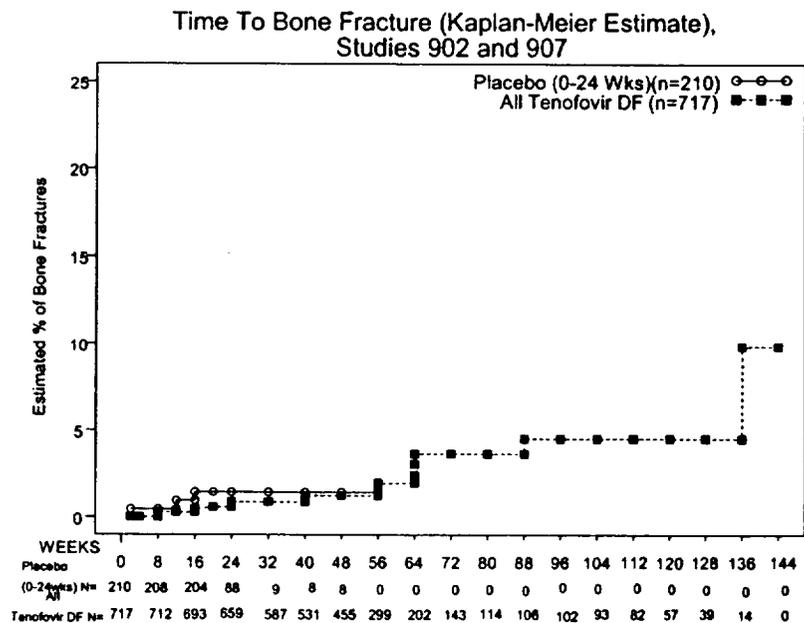
Summary of Bone Fracture Rates by Six Month Time Interval—  
 Studies 902 and 907

Time Interval (Months)	Placebo				All Tenofovir DF (75mg, 150mg, 300mg)				
	Number of Patients	Number of Fractures	Total Exposure (person-years)	Fracture Rate (95% CI)	Number of Patients	Number of Fractures	Total Exposure (person-years)	Fracture Rate (95% CI)	Odds Ratio (95% CI)
0-6	210	3	95	3.2	717	6	348	1.7	1.0 (1.0,1.0)
>6-12	11	0	4	0.0	635	2	263	0.8	0.4 (0.1, 2.2)
>12-18	4	0	0.1	0.0	352	5	100	5.0	2.9 (0.9, 9.5)
>18-24					119	1	52	1.9	1.1 (0.1, 9.3)
>24					92	1	35	2.9	1.6 (0.2, 13.8)

Note: Odds Ratio for a given six-month time interval was computed for the base comparison of 0-6 months.

Source: FDA Analysis based on safety update data on bone fractures in NDA 21-356, SN 047.

In summary, based on the odds ratios, there did not appear to be a conclusive pattern of increase in bone fracture rates over a six-month time interval through the first two years (p-value for trend test was 0.271).

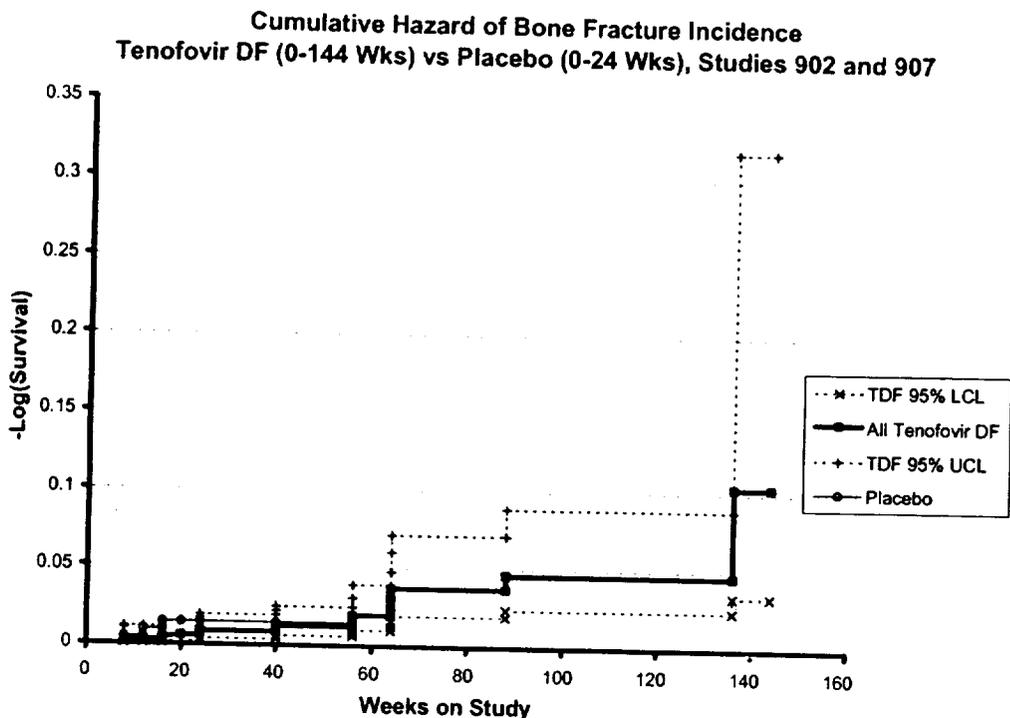


Source: FDA Analysis based on safety update data on bone fractures in NDA 21-356, SN 047.

Figure 5: Time to Bone Fracture (Kaplan-Meier Estimate)—Studies 902 and 907

The Kaplan-Meier curve in Figure 5 shows an estimate of the percentage of bone fractures over time (0-144 weeks). Beyond 2 years, the number of patients followed is very sparse after which the estimated curve will not be very reliable. Through the first two years the Kaplan-Meier curve estimates a bone fracture of approximately 4.5% in the Tenofovir DF with a 95% confidence interval of (1.6%, 7.3%). Note that only 93 patients were followed through Week 104 (~2 years). The estimated fracture rate may vary as data on more patients followed for 2 years is available.

Consistent with the previous approach of Poisson regression, the Kaplan-Meier curve indicates that there may be an increase in bone fracture rates between 1 year to 2 years (see Weeks 52 to 104 in Figure 5). The odds ratio for the time interval >12-24 months as compared to the first year (0-12 months) was 2.99 with a 95% confidence interval of (1.04, 8.64). This gives marginal indication that the incidence of bone fractures may be higher in the second year than in the first year. Again, this evidence is not conclusive due to the relatively small incidences observed in the clinical studies 902 and 907.



Source: FDA Analysis based on safety update data on bone fractures in NDA 21-356, SN 047.

Figure 6: Cumulative Hazard of Bone Fractures over Time—Studies 902 and 907

Figure 6 shows the estimated cumulative hazard of bone fractures over time in the Tenofovir DF and Placebo groups. The cumulative hazard function for Tenofovir DF shows that during the first 24 weeks, the hazard of bone fractures is similar between Tenofovir DF and Placebo (See the solid bold line with squares for Tenofovir DF and solid line with circles for Placebo which are parallel in the first year). Also, the hazard of bone fractures in both groups remains fairly low in the first 1 year. Between one to two years, the hazard rate in the Tenofovir DF group appears slightly higher than in the first year, because the slope of the cumulative hazard line in the second year (52-104 weeks) for Tenofovir DF appears higher than the slope of the cumulative hazard line in the first one year (0-52 weeks).

## **E. Statistical Reviewer's Summary**

Based on all the available efficacy data through Week 24 (and beyond) and the safety data through Week 144 in Studies 902 and 907, we conclude the following.

1. Studies 902 (a Phase 2 dose-ranging study) and 907 (Phase 3 study) enrolled treatment-experienced HIV-infected patients in the United States, Europe and Australia who were predominantly male (92% in 902 and 85% in 907) with median age of approximately 40 years. In Study 902 (n=186) and 907 (n=550), respectively, the mean baseline HIV-1 RNA was 4,571 copies/mL and 2,291 copies/mL; the mean CD4+ cell count was 374 cells/mm<sup>3</sup> and 427 cells/mm<sup>3</sup>; and the median duration of prior antiretroviral use among these patients was 4 years and ~5 years.
2. The time-weighted mean change from baseline at Week 24 (DAVG<sub>24</sub>) in Study 902 showed a dose-response as the dose of Tenofovir DF increased from 75 mg to 150 mg and 300 mg when compared to Placebo. The net reduction in viral load was greater as the dose of Tenofovir DF increased. The net mean reduction in viral load at Week 24 (mean DAVG<sub>24</sub>) due to the chosen dose of Tenofovir DF 300 mg was  $-0.54 \log_{10}$ , favoring Tenofovir DF 300 mg to Placebo.
3. Study 907 also showed primary efficacy results in favor of Tenofovir DF 300 mg. The net mean reduction of viral load at Week 24 (DAVG<sub>24</sub>) due to Tenofovir DF 300 mg was  $-0.56 \log_{10}$ , favoring Tenofovir DF versus Placebo.
4. Patients in the Placebo group in both studies crossed-over to Tenofovir DF 300 mg beyond 24 weeks, after which a comparison of efficacy was not available.
5. With respect to the secondary endpoint of proportion of patients achieving <400 copies/mL and <50 copies/mL (missing values treated as failures and addition/change of background therapy regarded as failures), Study 902 did not show any significant difference between each of the Tenofovir DF arms versus Placebo. However, in Study 907, a greater proportion of patients achieved <400 copies/mL or <50 copies/mL at Week 24 in the Tenofovir DF 300 mg group as compared to Placebo. The observed treatment difference, TDF 300 mg vs Placebo, was 29% with a 95% confidence interval of (22%, 37%) for the endpoint related to <400 copies/mL and 19% with a 95% confidence interval of (13%, 24%) for the endpoint related to <50 copies/mL.
6. In Study 902, there was no consistent pattern of either increase or decrease in CD4+ cell counts through Week 24 in either the Placebo group or any of the three Tenofovir DF (75mg, 150mg, or 300mg) groups relative to Placebo. The same was true with the treatment difference in CD4+ cell counts between each of the Tenofovir DF groups versus Placebo. At best, the mean increase in CD4+ cell counts at any time point in any group was about 20 cells/mm<sup>3</sup> which is a modest increase when compared to the standard deviation of about 200 cells/mm<sup>3</sup>.
7. In Study 907, the overall trend in CD4+ cell count showed a modest and consistent

- increase through Week 32 in favor of Tenofovir DF 300mg. After Week 32, the number of patients followed decreased, making it difficult to interpret whether the trend will hold through Week 48. The mean change from baseline in CD4+ cell count at Week 24 was approximately +12 cells/mm<sup>3</sup> in the Tenofovir DF group and -5 cells/mm<sup>3</sup> in the Placebo group.
8. Assessment of the efficacy of Tenofovir DF 300 mg in subgroups of patients based on their baseline viral load, baseline CD4+ cell count, and the number of prior antiretroviral drugs used by these treatment-experience patients was also made. These subgroups were the randomization strata in the two studies.
    - a) Studies 902 and 907 showed that patients who had baseline viral load <5,000 copies/mL had greater reduction in viral load (DAVG<sub>24</sub> = -1.01 log<sub>10</sub> in 902 and -0.62 log<sub>10</sub> in 907) as compared to patients with baseline viral load ≥5,000 copies/mL (DAVG<sub>24</sub> = -0.31 log<sub>10</sub> in 902 and -0.45 log<sub>10</sub> in 907).
    - b) Similarly, a greater reduction in viral load was seen in patients with ≥200 cells/mm<sup>3</sup> (DAVG<sub>24</sub> = -0.62 log<sub>10</sub> in 902 and -0.60 log<sub>10</sub> in 907) as compared to patients with <200 cells/mm<sup>3</sup> (DAVG<sub>24</sub> = -0.57 log<sub>10</sub> in 902 and -0.44 log<sub>10</sub> in 907).
    - c) For patients who had previously used either <4 drugs or ≥4 drugs, the results were not consistent between Study 902 and 907. In Study 902, patients who had previously used <4 drugs had a smaller reduction of DAVG<sub>24</sub> = -0.35 log<sub>10</sub> vs -0.97 log<sub>10</sub> in patients who had prior ARV use of ≥4 drugs. Study 907 showed a greater reduction in viral load in patients who had previously used <4 drugs of DAVG<sub>24</sub> = -0.80 log<sub>10</sub> vs -0.54 log<sub>10</sub> in patients who had prior ARV use of ≥4 drugs.
    - d) Results seen in each of the above subgroups may have been confounded with the resistance pattern because patients in both studies were treatment-experienced.
  9. Genotypic analyses of the virology substudies of 902 and 907 showed that Tenofovir DF 300 mg showed an antiviral effect when either or both of AZT-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) or M184V mutation was present at baseline. In the absence of AZT-associated mutations, patients with the M184V mutation showed a -0.84 log<sub>10</sub> copies/mL decrease in their HIV RNA relative to placebo as compared -0.23 log<sub>10</sub> copies/mL decrease in HIV RNA for patients with wild-type 184. In the presence of AZT-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to Tenofovir DF 300 mg.
  10. Finally, a safety assessment of the incidence of bone fractures in all Tenofovir DF groups in Studies 902 and 907 (combined) was made. There was no conclusive pattern of increase in bone fracture rates over six-month intervals in the first two years. However, there was some suggestive evidence of increase in the incidence of bone fractures in the Tenofovir DF group between first year and second year, as compared to the first year.

**References**

1. Hochberg, Yosef. 'A sharper Bonferroni procedure for multiple tests of significance', *Biometrika*, 75, 800-803 (1988).
2. Rosner, Bernard. *Fundamentals of Biostatistics*, 5<sup>th</sup> edition, Duxbury, 2000.

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HFD-725/StatDivDir/M. Huque  
HFD-700/OBDepDir/C. Anello

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