CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-356

MEDICAL REVIEW

Medical Review
NDA 21-356
Tenofovir DF for the Treatment of HIV-1 Infection

Pre Submission Date:	March 21, 2001
Submission Date:	May 1, 2001
Date Completed:	November 7, 2001
Applicant:	Gilead Sciences, 333 Lakeside Drive Foster City, CA 94404
Drug:	Chemical: 9-[(R) - 2[[bis[[(isopropoxycarbonyl)osy]methoxy]phosphinyl]methoxy]propyl]adenine
Generic:	Tenofovir disoproxil fumarate (DF)
Trade:	Viread
Dosage and Form:	300 mg tablets once daily
Indication:	Tenofovir DF is indicated for the treatment of HIV infection
Related INDs:	[redacted]

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Executive Summary

This executive summary contains the Recommendations and the Summary of Clinical Findings for NDA 21-356, VIREAD (tenofovir DF) for the treatment of HIV-1 Infection.

A. Recommendation on Approvability

Accelerated approval should be granted for tenofovir DF tablets. This NDA application provides clear evidence of the antiviral activity of tenofovir when added to a stable background regimen for 24-48 weeks. In two pivotal studies, statistically significant reductions in HIV RNA were observed in antiretroviral experienced patients treated with tenofovir 300 mg daily. These results are noteworthy given that the majority of approvals have been based primarily on studies in treatment-naïve patients. For many drugs, there is a need for more data characterizing their activity in treatment-experienced patients with prior exposure to the same drug class. Studies submitted in this NDA demonstrate a favorable safety and efficacy profile for patient populations at need for other treatment options. In sum, information contained in this application fulfills the intent of the accelerated approval regulations.

B. Recommendation on Phase 4 Studies

1. Accelerated Approval Commitments

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. Applicants are required to conduct post-marketing studies under Subpart H. The applicant agreed to submit the results of two 48-week phase 3 studies of the safety and efficacy of tenofovir DF to support traditional approval. Study GS-903, "A Phase III, Double-Blind, Randomized, Active-Controlled, Multicenter Study of the Treatment of Antiretroviral-Naïve HIV-1 Infected Patients comparing Tenofovir Disoproxil Fumarate Administered in Combination with Lamivudine and Efavirenz Versus Stavudine, Lamivudine, and Efavirenz," is currently underway. Study GS-01-928, "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir Plus An optimized Background Regimen (OBR) Versus OBR Alone in HIV-1 infected, Antiretroviral Treatment-Experienced Children," is expected to begin enrollment in March 2002.

In addition the applicant is required to submit complete analyses of the safety data with respect to bone effects from studies 903 and 928. For study 928, the applicant will collect data on BMD and laboratory parameters specific to bone metabolism, including but not limited to osteocacin, bALP, N and C-teleopeptide, vitamin D and PTH. The final study reports for both studies should include detailed analyses of the BMD results and the laboratory parameters specific to bone metabolism, including but not limited to osteocalcin, bALP, N and C- teleopeptide, vitamin D and PTH. The final study reports for GS-00-903 and GS-01-928 should include analyses for these parameters through week 96 and 48, respectively. In addition, the final study report for study 903 should include analyses to address the potential for long term renal toxicities (through week 96).

2. Phase 4 Commitments

1. Conduct genotypic and phenotypic analysis of clinical isolates from all adult and pediatric patients in Studies 903 and 928 who experience loss of virologic response.
2. Evaluate the virologic response of VIREAD in patients with baseline reduced susceptibility to didanosine and abacavir. Isolates with mutations conferring resistance to didanosine or abacavir should be evaluated in order to discern meaningful differences in virologic response.

3. Characterize the role of the K65R mutation in conferring resistance to VIREAD and cross resistance between VIREAD and other nucleoside reverse transcriptase inhibitors, specifically didanosine, abacavir and zalcitabine.

4. Investigate whether the M184V increases virologic response, if present alone or in combination with other NRTI mutations. Isolates should be evaluated in order to discern meaningful differences in virologic response.

Pharmacology/toxicology

5. Carcinogenicity studies in rats and mice.

Clinical Pharmacology:

6. Evaluation of VIREAD pharmacokinetics in subjects with renal insufficiency, to allow the determination of dosing recommendations.

7. Measurement of concentrations of tenofovir disoproxil and mono-POC PMPA relative to tenofovir in vivo.

8. Characterization of the specific renal transport pathways of tenofovir in-vivo (anionic vs. cationic transport). Once determined, an evaluation of the potential for drug interactions between VIREAD and drugs that are renally eliminated and frequently used by the HIV population should be conducted. Specific examples may include: acyclovir, valacyclovir, ganciclovir, valganciclovir and cidofovir. The study design should mimic clinical conditions with regard to dosing with/without food.

9. Conduct drug interaction studies between VIREAD and enteric-coated didanosine, methadone, oral contraceptives and [redacted] The study designs should mimic clinical conditions with regard to dosing with/without food.

10. A drug interaction study including VIREAD and lopinavir/ritonavir to confirm lopinavir/ritonavir PK changes observed in Study 909. The study design should mimic clinical conditions with regard to dosing with/without food. If these pharmacokinetic changes are confirmed Gilead will conduct a drug interaction study between VIREAD and ritonavir 400 mg to characterize the drug interaction between VIREAD and higher doses of ritonavir.

Clinical

11. Evaluation of the activity (hepatitis B DNA, hepatitis e antigen seroconversion and effect on transaminases) and safety of VIREAD for the treatment of hepatitis B infection in patients who are coinfected with HIV and hepatitis B. Specifically, the occurrence of hepatitis flares in patients who discontinue VIREAD treatment will be monitored. The occurrence of tenofovir associated hepatitis B resistance should also be evaluated. The above parameters should be evaluated in patients receiving the combination of lamivudine and VIREAD for the treatment of hepatitis B. Approximately 100 patients receiving VIREAD-containing regimens should be evaluated from planned and ongoing studies. Data from comparator arms should also be submitted for review.

12. Long-term safety monitoring for serious adverse events and fractures in study 910, including BMD changes in patients participating in the BMD substudy. This study will follow approximately 575 patients for up to 4 years.

C. Risk Communication

Potential safety risks are bone effects, lactic acidosis/hepatic steatosis, and dosing patients with underlying renal insufficiency. Presenting these concerns at an open-public meeting before the Division of Antiviral Drug Products Advisory Committee was the initial forum for risk communication. In addition, statements will be included in the label to communicate these known and potential risks.

Bone Toxicity:

One of the long term safety concerns for tenofovir is the potential for bone abnormalities. Therefore an advisory committee meeting was held to discuss this issue. At the meeting, we presented our findings of the non clinical and clinical data with regard to bone effects. In addition, we specifically asked the committee and the invited experts in bone metabolism to provide their assessment of the non clinical and clinical data with regard to bone effects and provide recommendations as to whether or not additional non clinical or clinical studies were needed in order to further evaluate tenofovir associated bone abnormalities.

The experts in bone metabolism felt that a mechanism for the bone toxicities had not been established. They suggested that future studies should assess several clinical laboratory tests, including vitamin D levels and specific bone biomarkers. The applicant is collecting all the suggested laboratory tests in study 903. The submission of the safety results from this study is part of the applicant's accelerated approval commitments.

In addition, since the potential for long term bone abnormalities is unknown and there is limited efficacy data in treatment naïve patients, some members felt that treatment with tenofovir should only be recommended for treatment experienced patients. Given these concerns, the INDICATIONS AND USAGE section of the package insert includes the following statement, "Studies in antiretroviral naïve patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined."

Additionally, several statements were included in the package insert regarding the animal toxicity data and clinical monitoring for potential bone effects.

Dosing Patients with Renal Insufficiency:

A warning regarding renal impairment was also included in the label. The rationale for this warning includes the following:

- tenofovir is principally eliminated by the kidney and a formal drug interaction study in patients with renal impairment was not conducted prior to NDA submission and
- patients with renal insufficiency (creatinine clearance < 60 mL/min) were excluded from the clinical trials

A pharmacokinetic study in patients with renal impairment is a phase 4 commitment. Based on the results on the study, this warning will be re evaluated.

Lactic Acidosis Class Warning:

A BOX WARNING and Warning for lactic acidosis and severe hepatomegaly was included in the package insert. These warnings are consistent with the other nucleoside reverse transcriptase inhibitor package inserts. The rationale for inclusion of the Box Warning is as follows:

- although in vitro studies may suggest a lack of mitochondrial toxicity, it is unclear if these results are predictive in vivo
- case reports of lactic acidosis in clinical trials and expanded access program were observed
- tenofovir is considered to function as a nucleoside analogue and therefore should carry the same class warnings as other NRTIs

SUMMARY OF CLINICAL FINDINGS

A. Overview of Clinical Program

Trade Name: Viread
Class: Nucleotide analogue
Formulation: Tablets
Dosage: 300 mg once daily

Number of important trials: Studies 902 and 907 were considered the pivotal studies for this NDA

Number of patients enrolled in these trials : Six hundred and seventy eight patients received at least one dose of tenofovir 300 mg, including placebo crossover patients in studies 902 and 907 and patients who initially received 75 mg or 150 mg for the first 48 weeks before rollover into the 300 mg arm in study 902.

Indications studied: Treatment of HIV infection

Overall number of patients exposed: Approximately 1057 patients received at least one dose of IV or oral tenofovir at the following doses; 1 and 3 mg/kg IV and 75, 150, 300 and 600 mg oral.

B. Efficacy Summary

The clinical activity of tenofovir has been demonstrated in treatment experienced patients. At the time of accelerated approval for other antiretroviral drugs, determination of efficacy was often based on studies conducted in treatment naïve patients. For this NDA, the applicant undertook a development program that evaluated treatment experienced patients with extensive nucleoside resistance (94%). In addition, approximately 50% of the patients studied had evidence of protease inhibitor resistance and 30-40% had NNRTI resistance at baseline. This patient population is at need for other therapeutic options and is often not included in registrational trials to support approval. Results from these studies provide important information for the treatment of HIV-1 infection and fulfills the intent of the accelerated approval regulations.

This NDA contains clinical data from four trials conducted with tenofovir tablets, including 2 pivotal studies (GS-98-902 and GS-99-907) and two supportive studies. Both pivotal studies were similar in design and evaluated the safety and efficacy of tenofovir versus placebo when added to a stable antiretroviral regimen in patients with prior nucleoside analogue experience. In addition, activity against nucleoside-resistant HIV was assessed in prospectively defined resistance subgroups.

In both studies statistically significant differences of approximately 0.5-0.6 $\log_{10}$ were observed for the primary efficacy endpoint ($DAVG_{24}$) favoring the tenofovir groups over placebo. In study 902, patients receiving 300 mg had sustained HIV RNA reductions over 48 weeks that were superior to those receiving either 150 mg or 75 mg. Numerically, greater HIV RNA decreases were observed with increasing doses in study 902.

In study 902, there were no statistically significant differences between the 4 treatment groups with respect to the proportion of patients achieving HIV RNA levels < 400 or < 50 copies/mL; however numerical differences favoring tenofovir 300 mg over placebo were observed. For patients with extensive prior antiretroviral therapy and/or higher baseline viral loads, the addition of one drug to a background regimen may not be expected to decrease HIV RNA to levels below assay limits. Also study 902 was not statistically powered to detect differences between groups for endpoints assessing proportions < 400 or 50 copies/mL.

In study 907, a greater proportion of patients in the tenofovir group achieved HIV RNA < 400 copies/mL compared to placebo. This study was adequately powered to detect differences between treatment groups for proportion < 400 or 50 copies/mL. In addition, baseline HIV RNA levels in this study were lower than that of study 902. With baseline HIV RNA levels in this range, the addition of one new drug is more likely to decrease levels below an assay limit.

In both pivotal studies increases in CD4 cell counts were modest. In study 902, the mean $DAVG_{24}$ for CD4 cell counts was –10.5 cells/mm^3 for the 300 mg group compared to –3 cells/mm^3 for the placebo group. Differences between treatment groups were not statistically significant. For study 907, there was a statistically significant difference in the $DAVG_{24}$ for CD4 favoring tenofovir. The mean $DAVG_{24}$ was +12 cells/mm^3 in the tenofovir group compared to –10 cells/mm^3 in the placebo group, resulting in a net treatment difference of approximately 20 cells/mm^3.

It is also important to note that the trial designs of studies 902 and 907 may not have been optimal for assessing changes in CD4 cell counts for treatment experienced patients. Similar results were reported for the abacavir CNA2003 study. CNA2003 was similar in design to tenofovir studies 902 and 907. The activity of abacavir versus placebo when added to stable antiretroviral regimens was evaluated in treatment experienced patients. No statistically significant differences for change in CD4 from baseline was noted between abacavir and placebo; however there was a numerical difference favoring the abacavir group (+30 vs +1 cells/mm^3). Results from studies CNA2003, 902 and 907 suggest that small changes in CD4 cell counts may be expected in treatment experienced patients with relatively stable CD4 cell counts at baseline. For these patients, the addition of one new agent to a stable background antiretroviral regimen did not produce substantial increases in CD4 cell counts over time. Further evaluations of CD4 cell counts in studies with different designs are needed.

The clinical virology data suggest the potential for some cross resistance between tenofovir and specific NRTI mutations. Tenofovir activity was diminished when three or more zidovudine-associated mutations, including the M41L, or L210W were present at baseline. Reduced susceptibility to tenofovir and ZDV at baseline also diminished tenofovir activity. No cross resistance between tenofovir and the lamivudine/abacavir-associated mutation (M184V) was detected.

Overall, the antiviral activity of tenofovir has been demonstrated in two pivotal studies. Statistically significant reductions in HIV RNA were observed over 24 weeks in antiretroviral experienced patients. In study 902, no significant differences for mean change in CD4 cell counts from baseline were noted between tenofovir and placebo. However in study 907 statistically significant differences favoring tenofovir were observed.

It will be important to determine if the response rates observed are sustained over 48 weeks. Studies 903 and 928 will be submitted to the division in support of traditional approval at a later time.

C. Safety Summary

1. Adequacy of safety testing

The safety of tenofovir has been evaluated in over 1,000 patients. In addition over 5,000 patients have received tenofovir through an expanded access program. In the two pivotal trials, 687 patients received at least one dose of tenofovir 300 mg, including placebo crossover patients in studies 902 and 907 and patients who initially received 75mg or 150 mg for the first 48 weeks before rollover into 300 mg in study 902. Patients were followed for adverse events and laboratory abnormalities every 4 weeks for the first 24 weeks then every 8 weeks thereafter. Both the size of the safety data base and the adequacy of patient monitoring and follow up is consistent with that of other antiretroviral agents that have been granted accelerated approval.

2. Common adverse events and laboratory abnormalities

Except for gastrointestinal events, the safety and tolerability of tenofovir was similar to that of placebo. Without regard to causality, the most common events reported were asthenia (19%), headache (14%), diarrhea (22%), nausea (20%) and pharyngitis (18%). There was a higher incidence of vomiting in the 300 mg group (12%) versus placebo (6%). This finding was statistically significant (p=0.0225). More patients randomized to tenofovir compared to placebo experienced GI events, including diarrhea (22% vs 17%), flatulence (6% vs 2%), nausea (20% vs 15%) and vomiting (12% vs 6%).

Grade 3+ laboratory abnormalities were similar between placebo and tenofovir with few exceptions. Triglyceride, creatinine kinase, amylase and serum glucose elevations occurred more frequently in the placebo group compared to tenofovir. Discontinuations due to laboratory abnormalities were similar between groups. The types of laboratory abnormalities noted during the trial are consistent with what is expected in patients receiving multiple antiretroviral agents.

3. Relationship of side effects to known animal toxicity

Please also refer to sections 10.2 and 10.8.4 for further details

Three major toxicities were detected in the animal studies; gastrointestinal, renal and bone abnormalities. Gastrointestinal events in humans have been well characterized in the phase 2/3 trials. Few patients discontinued study drug due to these events.

Nonclinical studies showed evidence of renal toxicity in 4 animal species, mouse, rat, dog and monkey. Kidney changes were associated directly with exposure to tenofovir. Renal tubular toxicity was noted after 56 days to 42 weeks of tenofovir treatment in the mouse, rat, dog and monkey. Interstitial nephritis was noted after chronic dosing in dogs. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed in varying degrees in these animals. These toxicities were noted at exposure levels 2-20 times higher than the human clinical exposures following administration of tenofovir at 300 mg/day. In addition, decreased renal clearance of tenofovir and a Fanconi-like syndrome with glucosuria and hypophosphatemia was noted in monkeys following a dose of 30 mg/kg (subcutaneously) for 11-24 months.

Given the nonclinical evidence for renal toxicity, renal events and laboratory abnormalities were monitored closely during the trials. With the available data, there does not appear to be any significant renal toxicity or renal related laboratory abnormalities associated with tenofovir use. It is important to note that another antiretroviral from the class of nucleotide analogues, adefovir, was associated with delayed nephrotoxcity. It will be important to assess long term changes in larger numbers of patients.

Reductions in bone mineral density were noted in three animal species following tenofovir administration. Bone mineral loss was noted in juvenile rhesus monkeys following ten months of subcutaneous administration of tenofovir 30 mg/kg/day. Decreased bone mineral content and density were observed in rats at oral doses of 300 and 1000 mg/kg and in dogs at doses of 30 mg/kg given for 13 or 42 weeks. Two possible mechanisms for bone abnormalities have been suggested. First, changes in bone mineral density are thought to be secondary to renal tubular reabsorption defects. Hypophosphatemia was observed in monkeys and hypercalciuria was seen in rats and dogs. Second, findings in rat and monkey studies suggest a direct drug-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. Preclinical studies show that renal tubular dysfunction and bone mineral losses are dose-related and generally reversible. Long term administration (up to 10 months) of low dose tenofovir or short term administration with high doses of tenofovir was not associated with bone abnormalities. Bone abnormalities were observed following chronic administration of intermediate and high doses of tenofovir. It is not known if chronic administration (> 42 weeks) of low dose tenofovir will cause bone abnormalities.

Review of exposure data and bone abnormalities noted in animal studies gives some reassurance that there is an adequate margin of safety for the 300 mg daily dose. AUCs of 18 μg*hr/ml, 30 μg*hr/ml and 97.9 to 240 μg*hr/ml in rats, dogs, monkey, respectively were noted in conjunction with bone abnormalities. The average AUC noted in humans receiving 300 mg once daily is 3.34 μg*hr/ml. Reductions in bone mineral density in rats and dogs were noted at exposure levels 6-10 times higher than the human clinical exposures following administration of tenofovir at 300 mg/day. Bone abnormalities in monkeys were noted at exposure levels 29-80 times higher than the human clinical exposures with tenofovir 300 mg. However, safety margins were lower at doses of tenofovir that elicited no effects in animal toxicology studies.

The variability of drug concentrations in humans were minimal over time, thus providing some assurance that individual patient exposures are not approaching those associated with bone abnormalities in the animal studies. Additionally no obvious increases in fracture rate over 6 month time intervals were seen.

4. Drug-Drug interaction potential

Tenofovir is not metabolized via the cytochrome P450 system, therefore interactions with agents metabolized by this system are unlikely. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion, with or without tubular reabsorption, therefore there may be competition with other agents that rely extensively on active tubular secretion for elimination. As a consequence, coadministration of tenofovir with drugs that decrease or compete for renal clearance may increase serum concentrations of tenofovir. The applicant did not conduct any formal drug interaction studies with agents that are renally eliminated. However, the applicant conducted a multiple-dose study investigating the pharmacokinetics of tenofovir disoproxil fumarate in combination with lamivudine, didanosine, indinavir, lopinavir/ritonavir, efavirenz in healthy volunteers. Clinically relevant drug interactions resulting in safety concerns or requiring dose adjustments for tenofovir or lamivudine, indinavir, lopinavir/ritonavir and efavirenz were not observed.

In a drug interaction study with tenofovir and didanosine, it was found that didanosine AUC and Cmax were increased by 44% and 24%, respectively. Tenofovir pharmacokinetics were unchanged. The mechanism for this interaction is unknown. This interaction may have clinical implications in that an increase in didanosine associated events could occur, specifically pancreatitis, peripheral neuropathy and GI intolerance. Clinicians should be aware of this interaction and the potential for increased didanosine related events. Please refer to section 10.2 for complete details on the applicant's and FDA's analyses.

5. Effect of trial exclusions on safety profile vs expected marketed population

Patients with renal impairment or those requiring concomitant use of nephrotoxic agents or agents that inhibit or compete for elimination via active tubular section were excluded from trial participation.
There may be a potential for increased serum concentrations of tenofovir in patients with renal impairment or in patients receiving drug prohibited in clinical trials. The risk of receiving prolonged tenofovir at higher concentrations is unknown. Post marketing studies to evaluate the pharmacokinetics of tenofovir DF in renally impaired patients and drug interaction studies with agents that are renally eliminated and frequently used by HIV infected patients were recommended to the applicant.

6. Recommended Warnings

BOX WARNING:

The following BOX WARNING was included in the label. This warning is consistent with the other nucleoside reverse transcriptase inhibitor package insert. The rationale for inclusion of the Box Warning is as follows:

- Although in vitro studies may suggest a lack of mitochondrial toxicity, it is unclear if these results are predictive in vivo
- Case reports of lactic acidosis in clinical trials and expanded access program
- Tenofovir is considered to function as a nucleoside analogue and therefore should carry the same class warnings as other NRTIs

WARNING
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

In addition, the following information was included in the Warning section of the package insert.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD ™ should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Tenofovir is principally eliminated via the kidney and the applicant has not conducted studies in patients with renal impairment therefore the following statement was included in the WARNING section of the package insert.

> VIREAD™ should not be administered to patients with renal insufficiency until further data become available describing the disposition of VIREAD ™ in these patients

7. Relationship of safety to other antiretroviral agents

The safety profile of tenofovir when added to a stable background antiretroviral regimen (SBR) has been compared to a SBR alone. No major differences were noted between the treatment

groups. Adverse events and laboratory abnormalities noted were consistent with that observed in patients receiving combination therapy. More GI events were noted in patients receiving tenofovir + SBR vs SBR alone.

8. Unresolved safety issues

It is unknown if long term administration of tenofovir will lead to the development of renal toxicities and bone abnormalities. The applicant is collecting longer-term safety data to determine if these events or any new safety concerns arise with continued dosing of tenofovir .

D. Dosing

1. Level of confidence for dose/regimen

The choice of the 300 mg dose is based on results from studies 901 and 902. In studies 901 and 902, decreases in HIV RNA were greater in the 300 mg compared to 75 mg and 150 mg dose groups. No differences in decreases in HIV RNA were noted between tenofovir 300 and 600 mg. Based on the pharmacokinetic, safety and activity data, the choice of 300 mg given once daily is appropriate.

2. Dose-toxicity and dose-response relationship

The adverse event profile was similar for all doses studied. No dose tresponse for toxicity was apparent.

A dose response trend for decreases in HIV RNA was observed between 75 mg, 150 and 300 mg. No differences were detected between the 300 mg and 600 mg dose. Similar to the dose response relationship, there was also a correlation between both Cmax and AUC with respect to virologic response.

3. Dose modification recommendations

No dose modifications for tenofovir or concomitant medications are proposed at this time, however studies in patients with renal impairment should be conducted in order to determine if any dose adjustments are necessary. Drug interaction studies with tenofovir and agents that are renally eliminated are needed in order to determine if any dose modifications are needed with tenofovir or concomitant medications.

4. Unresolved dosing/administration issues

Dosing recommendations for pediatric patients and patients with renal impairment are needed. The applicant has adequately outlined the pediatric development program and also plans to conduct a pharmacokinetic study in patients with renal impairment. In addition, several drug interaction studies are needed. Please refer to post marketing commitments.

E. Special Populations

1. Age/Gender/Ethnic/Racial Analysis

No differences in efficacy were noted across the demographic subgroups evaluated. No clinically important safety differences were noted across the demographic subgroups. Numerically more males experienced diarrhea compared to females.

2. Other Special Populations

Geriatrics
Clinical studies of tenofovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects

Renal impairment:

Tenofovir is primarily eliminated via the kidney. The applicant did not conduct a study in patients with renal impairment, therefore appropriate dosing in this population is not available. The label includes a statement that tenofovir should not be administered to patients with renal insufficiency until further data becomes available. Also the label includes a statement that coadministration of tenofovir with drugs that decrease or compete for renal clearance may increase serum concentrations of tenofovir.

Hepatic impairment:

The pharmacokinetics of tenofovir in patients with hepatic impairment have not been determined. Since tenofovir is not metabolized by the liver, the impact of liver impairment should be minimal. However, because VIREAD is not entirely renally excreted (70-80%), tenofovir pharmacokinetics may be altered in hepatic insufficiency. The applicant has proposed a study in patients with hepatic impairment.

3. Status of pediatric studies and pediatric plan

The applicant is working diligently to collect pharmacokinetic data in pediatrics. Two single center studies to assess single and multiple dose pharmacokinetics in pediatrics patients are scheduled to begin in September and October 2001. The applicant is also committed to collecting pharmacokinetic data in children who receive tenofovir on a compassionate use basis. The applicant has also proposed an efficacy study in treatment experienced children for their required second confirmatory study for traditional approval.

Of note the pediatric development program was delayed until September 2001. Reports of bone loss and osteomalacia observed in animal studies were brought to the Division's attention early in tenofovir's development. As a consequence the Division and the applicant agreed that studies in pediatric patients, in which manifestations of bone toxicity could be more severe, would be delayed until these safety issues could be addressed in adults. Please refer to section 10.2 for further details.

4. Pregnancy use information

This product received a pregnancy category B rating. Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Viread should be used during pregnancy only if clearly needed.

The applicant was strongly encouraged to participate in the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry is an inter-company collaboration set up to monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral therapy.

Clinical Review

1. Regulatory History and Introduction

Regulatory History:

The first IND for tenofovir was submitted on March 19, 1997. An End-of-Phase-2 Meeting was held on October 22, 1999, to discuss the dose selection for further phase 3 development. On December 13, 1999, a teleconference was held to discuss the applicant's proposed filing strategy for an NDA for the treatment of HIV infection. The original filing plans included studies in both treatment experienced patients (studies 902 and 907) and treatment naïve patients (study 903). During this time the Division requested that the applicant include a bone safety analysis on a subgroup of patients in the phase 3 trials.

On September 6, 2000, the Division met with the applicant to discuss their revised plans for accelerated approval for tenofovir to treat patients who have failed or are resistant to other nucleoside analogues. In a subsequent correspondence, the Division stated that it was not yet possible to provide a definitive response regarding the acceptability of the revised plan for accelerated approval. At that time, there was insufficient information to adequately assess the risk versus benefit profile for tenofovir with respect to bone toxicity. The Division recommended that a summary of the 24-week efficacy data from study 907 and further non clinical and longer term clinical safety data be submitted for review. The Division felt that this information was needed to provide more definitive advice regarding the acceptability of the applicants revised NDA filing strategy. At that time the need for 48-week comparative bone toxicity data and 24-week efficacy results from study 903 in an NDA filing would be discussed.

A subsequent pre NDA meeting was held on April 20, 2001 to discuss the revised NDA filing plans for accelerated approval. During this meeting, the applicant provided a detailed summary of the amount of efficacy and safety data that would be available at the time of NDA filing and during the safety update. It was agreed that data from 902 and 907 would serve as the principal studies in support of accelerated approval. The amount of safety data appeared to be sufficient to evaluate fracture rates.

On May 1, 2001, the applicant submitted a NDA for accelerated approval for VIREAD (tenofovir DF), a nucleotide reverse transcriptase inhibitor, for the treatment of HIV infection. In support of the request for accelerated approval, the applicant submitted two principal studies evaluating the safety and efficacy of tenofovir when added to a stable background regimen for 24-48 weeks. In addition these studies evaluated HIV RNA response rates by baseline genotype and phenotype in prospectively defined subgroups. Three supportive studies were also submitted. One study evaluated single and multiple dose pharmacokinetics, safety and activity of IV tenofovir over 7 days. The second supportive study evaluated the safety and activity of 4 doses of tenofovir over 35 days. Lastly, a compassionate use study evaluating the safety of tenofovir in patients with limited therapeutic options was submitted in support of accelerated approval. Studies in pediatric patients are ongoing.

2. Relevant Reviews from Other Disciplines

2.1 Chemistry

Please refer to CMC review by Dr. Rao Kambhampati for further details. In sum, tenofovir disoproxil fumarate is a salt of a prodrug of tenofovir. Tablets containing 300 mg of tenofovir disoproxil fumarate are proposed for marketing.

2.2 Pharmacology/Toxicology:

The major toxicities identified in 3 animal species include gastrointestinal and renal toxicity and bone abnormalities. A summary of the renal and bone abnormalities is included in sections 10.2 and 10.8.4. Gastrointestinal toxicities were also noted in clinical trials. More patients randomized to tenofovir compared to placebo experienced GI events, including diarrhea, flatulence, nausea and vomiting. Please also refer to reviews by Drs. Pete Verma and Bruce Schneider.

2.3 Microbiology:

Please refer to Dr. Narayana Battula's review for information regarding in vitro antiviral activity, resistance and cross resistance. Results from the clinical virology substudies can be found in section 9.

3. Pharmacokinetics and Pharmacodynamics/Dose Selection

Please refer to Dr. Jooran Kim's review for detailed information regarding pharmacokinetics.

The pharmacokinetics of tenofovir are dose proportional over the dose range evaluated (75 mg, 150 mg , 300mg and 600 mg). The applicant also explored dose exposure-response relationships in study 901. In this study decreases in HIV RNA were greater in the 300 mg compared to 75 mg and 150 mg dose groups. No further HIV RNA reductions were observed for the 600 mg dose in study 901. The applicant noted comparisons of AUC_{ss} and Cmax demonstrated similar relationships with antiviral effect. Also in study 902, decreases in HIV RNA were greater in the 300 mg compared to 75 mg and 150 mg dose groups. Based on pharmacokinetic, safety and activity data from studies 901 and 902, the choice for the 300 mg once daily dose is appropriate.

4. Description of Data Sources

4.1 Primary Data

This NDA contains clinical data from 5 trials conducted with tenofovir, including 2 pivotal studies and 3 supportive studies. The clinical submission consists of 110 volumes of study documents and electronic datasets, Case Report Tabulations and Case Report Forms. Clinical efficacy and safety data from the 2 pivotal studies were provided in SAS transport file format on CD-ROM.

The pivotal studies are GS-98-902 and GS-99-907. Both studies were similar in design and evaluated the safety and efficacy of tenofovir versus placebo when added to a stable antiretroviral regimen. Activity against nucleoside-resistant HIV was assessed in prospectively defined resistance subgroups.

Three supportive studies were also submitted. Study 701 evaluated the safety, pharmacokinetics and activity of single and multiple doses (1 mg/kg and 3 mg/kg) of tenofovir when administered by IV infusion. Study 901 investigated 5 doses of tenofovir vs placebo in treatment naïve and experienced patients for 35 days. Study 908 was a compassionate use safety study in patients with limited therapeutic options. Summaries of the trials are provided in Table 4.1.A.

Table 4.1.A Summary of Clinical Trials

Study #	Design	Regimens	# Enrolled	Pt Population	Entry CD4 criteria	Entry RNA criteria	Duration of Treatment	Endpoints
701	Randomized Double-Blind Placebo Controlled	IV 1mg/kg IV 3 mg/kg Placebo	20	HIV +	≥ 200	≥10,000	7 days	Safety, PK, RNA and CD4
901	Randomized Double-Blind Placebo Controlled Dose Escalation	75 mg 150 mg 300 mg 600 mg 75 mg +HU Placebo	Blinded: N=59 Extended dosing N=7	HIV+	≥ 200	≥10,000	Blinded: 28 days Extended dosing: 12 months	Safety, PK, RNA and CD4
902	Randomized Double-Blind Placebo Controlled	75 mg 150 mg 300 mg placebo	Blinded: N=189 Extended dosing N=135	Tx experienced Must be on stable antiretroviral regimen	None	≥ 400 & ≤ 100,000	48 weeks Extended dosing: 12 months	RNA, CD4, safety, bone density
907	Randomized Double-Blind Placebo Controlled	300 mg Placebo	552	Tx experienced Must be on stable antiretroviral regimen	None	≥ 400 & ≤ 10,000	48 weeks	RNA, CD4, safety
908	Open label Safety Study	300 mg	291	Tx experienced Must be on stable antiretroviral regimen	≤ 50 or >50 and < 200 with OI	≥ 10,000	96 weeks	Safety
910	Open Label Roll-over protocol	300 mg	335 target 614	Previous TNF study participation	None	None	Until marketed	Long-term safety

4.2 Post-marketing experience

Tenofovir has not been marketed in any country. NDAs were submitted to the US and Europe in May 2001.

5. Review Methods

The medical review is based on the evaluation of NDA Section 8, which includes study reports for the individual pivotal and supportive trials and the Integrated Summary of Efficacy and Safety. The applicant's safety and efficacy analyses were confirmed by independent FDA analysis of the data. Dr. Rahia Bhore performed the efficacy analyses for the primary and selected secondary endpoints in the pivotal trials. Dr. Bruce Schneider from the Division of Metabolic and Endocrine Drug Products provided a consult for the review of all bone abnormalities and relevant laboratory findings.

For this review the study design, patient demographics, adverse events, laboratory data, efficacy and virology results were reviewed in detail for the primary studies, 902 and 907. Studies 701 and 901 were not reviewed in detail because these studies only provided short term efficacy data. However, patients in studies 701 and 901 were rolled over into a long term safety study, therefore additional safety data was reviewed. Long term safety was also reviewed for study 908. JMP Statistical Discovery software was used to evaluate the efficacy, virology and safety data. In this

review, tables that were derived from the applicant's presentation of the data are cited in the table footnotes while those that are derived from reviewer-generated results are not referenced.

The integrated summary of efficacy and safety contains pooled data from studies 902 and 907, when appropriate. In addition safety data from study 908 is summarized separately unless otherwise noted.

DSI audits were requested for the following studies and clinical sites. Study 907: Stephen Becker, MD, Pacific Horizon Medical Group San Francisco, CA; Nicholaos C. Ballos, MD Southwest Infectious Disease, Dallas, TX; Gerald Pierone, Jr, MD, The Treasure Coast Infectious Disease Consultants Vero Beach, FL; Study 902: Robert A. Myers, MD, Phoenix Body Positive, Phoenix, AZ.

DSI audit reports were received for these investigators. Minor violations were noted and did not appear to affect the quality of the data submitted.

Financial disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that all investigators and subinvestigators from studies 902 and 907 disclose proprietary interest or significant equity as defined in the regulations. The applicant has included a list of all investigators and subinvestigators who responded to their request on the form 3454. Only one investigator failed to complete the financial disclosure form. This investigator did not enroll any patients in the studies and discontinued study participation prior to completing the required forms. The applicant certified that none of the investigators for studies 902 and 907 received significant payments or entered into any financial arrangement with the applicant as outlined on this form.

6 Review of Efficacy

6.1 Clinical Trial GS-98-902

"A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Antiviral Activity of the Addition of Tenofovir DF to Combination Antiretroviral Regimens in Treatment-Experienced HIV-Infected Patients"

6.1.1. Study Design

Study 902 was a randomized, double-blind, placebo-controlled, dose ranging study that evaluated the efficacy and safety of tenofovir versus placebo when added to stable antiretroviral regimens. Subjects between the ages of 18 and 65 years of age, with plasma HIV-1 RNA levels $\geq$ 400 and $\leq$ 100,000 copies/mL, and currently receiving a stable antiretroviral regimen for at least 8 weeks were enrolled into the trial. A stable regimen was defined as standard antiretroviral therapy consisting of no more than 4 active agents. Subjects were randomized in a 2:1:1:1 ratio to add either tenofovir at one of 3 doses (300 mg, 150 mg or 75 mg, respectively) or placebo to their existing regimen.

Patients were encouraged to continue their baseline regimens, for at least four weeks postrandomization. However, changes in baseline regimens were permitted. At 24 weeks patients randomized to placebo were offered tenofovir 300 mg once daily in a blinded fashion, for the remainder of the 48 week study. At week 48 all subjects were offered tenofovir 300 mg QD and continued in the open label phase of the trial.

Study subjects were seen at Weeks, 2, 4, 8, 12, 16, 20, 24, 28, 32, 40, 44, 48. The study was then extended through week 72. Subjects were then enrolled to study 910, an open label roll over protocol to assess long term safety in patients who participated in previous tenofovir trials.

Adverse events, physical exam, laboratory monitoring for toxicity, and immunologic and virologic assessments of efficacy were performed at regular intervals. Selected patients received bone densitometry, vitamin D, testosterone and PTH levels.

Adverse Events and laboratory abnormalities were assessed by the standardized ACTG Toxicity Grading Table. Based on preclinical evidence of nephrotoxicity, patients were permanently discontinued from study drug for a confirmed serum creatinine > 2.0 mg/dL. Patients were also permanently discontinued from study drug for all drug related grade 4 events. There were no criteria for study drug discontinuation due to lack or loss of virologic response.

6.1.2. Analysis Plan

The primary efficacy endpoints were the time-weighted change in $\log_{10}$ HIV RNA at week 4 ($DAVG_4$) and week 24 ($DAVG_{24}$) and mean change from baseline for CD4 cell counts. Secondary endpoints included $DAVG_{48}$, HIV RNA mean change from baseline, proportion < 400 and < 50 copies/mL, proportion with $\geq$ 1 log decrease in HIV RNA at week 24 and 48, number of patients with at least one change in background regimen and number of changes and time to first change in background regimen. Evaluations of HIV RNA were made with two FDA approved assays: HIV-1 Monitor Test for screening values and Ultrasensitive HIV-1 Monitor Test for all post screening values.

The primary and secondary endpoints were assessed for differences among the four treatment groups. The time-weighted change from baseline was calculated using the trapezoidal rule with all available post baseline data minus the baseline average. The primary analysis was performed using the intent to treat (ITT) population. The ITT analysis grouped subjects according to randomized treatment and utilized all follow-up data.

The primary safety endpoint was the incidence of patients with grade 3 or greater adverse events and laboratory abnormalities. The secondary safety endpoints were the proportion of patients who discontinued study drug due to adverse events, time to first study drug dose modification and time to study drug discontinuation and changes in weight and Karnofsky performance status. All patients who received at least 1 dose of study drug were assessed for safety. Treatment-emergent events were compared between arms using COSTART terms. In addition all bone fracture events regardless of cause or severity were evaluated in conjunction with all relevant laboratory data and prior medical histories.

6.1.3. Study Population and Patient Disposition

A total of 189 patients were enrolled and 186 patients received at least 1 dose of study drug. Twenty-one patients in the placebo group received tenofovir 300 mg after week 24. A total of 135 patients were in the open-label extension phase. All patients received tenofovir 300 mg after week 48.

Baseline demographics are displayed in Table 6.1.3.A. The baseline demographic characteristics were similar for all treatment groups. Patients were predominantly male (94%), Caucasian (74%), median age of 41 years (27-60) with a mean HIV RNA of 3.7 $\log_{10}$ copies/mL and mean CD4 cell count of 381 cells/mm^3. Of note 50% of subjects had AIDS. The overall mean duration of prior antiretroviral therapy was 55 months.

Table 6.1.3.A. Demographics and Baseline Characteristics

		TENOFOVIR		
	Placebo (N=28)	75 mg (n=53)	150 mg (n=51)	300 mg (n=54)
Age mean (range)	41 (30-56)	43 (29-62)	42 (27-60)	41 (27-60)
Sex – male %	26 (93%)	46 (87%)	48 (94%)	51 (94%)
Race/Ethnicity				
Caucasian	20 (71%)	37 (70%)	41 (80%)	40 (74%)
African American	3 (11%)	7 (13%)	4 (8%)	10 (19%)
Hispanic	2 (7%)	9 (17%)	6 (12%)	4 (7%)
Native American	1 (4%)	0	0	0
Other	2 (7%)	0	0	0
Baseline HIV Labs – mean				
Log HIV RNA	3.8	3.6	3.6	3.7
CD4 cell count	298	374	410	381
Mean Prior Antiretroviral Use - months	54	58	54	54

All patients received at least two antiretrovirals as part of their background therapy at baseline. There were no differences in the number or type of antiretrovirals in the background therapy among the treatment groups. Forty percent of subjects received 1 PI and 2 RTIs.

Baseline genotypic data was available for 184 patients. Ninety-four percent, 57%, and 32% of patients had mutations associated with RTIs, PIs and NNRTIs, respectively. The incidence of mutations was similar across all treatment groups. See Review of Clinical Virology Section for further details

The proportion of patients discontinuing treatment and the primary reasons for discontinuation from the tenofovir arms are summarized in Table 6.1.3.B. Of note, the protocol did not mandate that patients discontinue due to lack of virologic response.

Table 6.1.3.B. Patient Disposition Through Week 48

	TENOFOVIR			
	75 MG	150 MG	300 MG	PLACEBO CROSSOVER (24-48 WEEKS)
# patients received at least 1 dose of study drug	53	51	54	21
Discontinued within 48 weeks	14 (26%)	12 (24%)	13 (24%)	2 (10%)
Reasons for Discontinuation				
AE/Intercurrent Illness	6 (11%)	5 (10%)	5 (9%)	0
Lost to Follow Up	3 (6%)	5 (10%)	3 (6%)	0
Lack of Virologic Response	2 (4%)	0	0	0
Noncompliance	0	1 (2%)	0	0
Death	1 (2%)	0	0	0
Other	2 (4%)	1 (2%)	5 (9%)	2 (10%)

Source: appendix 12.3.1, table 6 and appendix 12.3.3, data listing 4 and table 6-2

An additional 26 patients (19%) discontinued in the open-label extension phase . The primary reasons for discontinuation from the tenofovir arms at in the open-label phase are displayed in Table 6.1.3.C.

Table 6.1.3.C. Patient Disposition Open Label Phase

	TENOFOVIR			
	75 MG / 300 MG (N=37)	150 MG / 300 MG (N=37)	300 MG / 300 MG (N=42)	PLACEBO CROSSOVER (N=19)
Number of patients who discontinued from open-label phase	6 (16%)	8 (22%)	6 (14%)	(32%)
Reasons for Discontinuation				
AE/Intercurrent Illness/Lab Toxicity	1 (3%)	2 (5%)	2 (5%)	1 (5%)
Lack of Virologic Response	2 (5%)	0	1 (2%)	0
Lost to Follow-Up	0	1 (3%)	1 (2%)	2 (11%)
Noncompliance	1 (3%)	0	0	0
Death	0	0	1 (2%)	0
Other	2 (5%)	5 (14%)	1 (2%)	3 (16%)

Source appendix 12.3.1, table 2 and table 6-1

One hundred and one patients (54%) were still receiving tenofovir as of the safety update cut off date. Overall treatment with tenofovir was well tolerated over the follow up time of 143 weeks.

Review of Efficacy:

Please refer to Dr. Bhore's statistical review for a comprehensive analysis of the final efficacy results.

The primary efficacy endpoints were the time-weighted change in $\log_{10}$ HIV RNA at week 4 ($DAVG_4$) and week 24 ($DAVG_{24}$) and mean change from baseline for CD4 cell counts. Secondary endpoints included $DAVG_{48}$, HIV RNA mean change from baseline, and proportion < 400 and < 50 copies/mL. For the proportion < 400 or < 50 copies/mL analyses, patients who added a new antiretroviral agent prior to week 24 were considered failures. Efficacy results for the HIV RNA endpoints are presented in Table 6.1.3.D.

Table 6.1.3.D. Summary of Efficacy HIV RNA

		TENOFOVIR		
	Placebo (N=28)	75 mg (n=53)	150 mg (n=51)	300 mg (n=54)
Mean $DAVG_4$	+0.02	-0.22	-0.44	-0.62
Mean $DAVG_{24}$	+0.02	-0.26	-0.34	-0.58
Mean $DAVG_{48}$	NA	-0.33	-0.34	-0.62
<400 copies/mL (week 24)	2/28 (7%)	5/53 (9%)	6/51 (12%)	10/54 (19%)
<50 copies/mL (week 24)	0/28 (0%)	2/53 (4%)	1/51 (2%)	6/54 (11%)

Decreases in HIV RNA from baseline were noted for all the tenofovir dose groups at the specified timepoints. There were statistically significant differences for each tenofovir group compared to placebo. Patients receiving 300 mg had sustained HIV RNA reductions over 48 weeks that were superior to those receiving either 150 mg or 75 mg. Numerically, greater HIV RNA decreases were observed with increasing doses in study 902.

No statistically significant differences between the 4 treatment groups with respect to the proportion of patients achieving HIV RNA levels < 400 or < 50 copies/mL were observed, however, numerical differences favoring tenofovir 300 mg were seen. It is important to note that for patients with extensive prior antiretroviral therapy and/or higher baseline viral loads, the addition of one drug to a background regimen may not be expected to decrease HIV RNA to

levels below assay limits. Of note, study 902 may not have been of sufficient size to detect treatment differences for the secondary endpoint of proportion below an assay limit.

The protocol permitted changes to background therapy after week four. Approximately 24% of patients added a new antiretroviral agent by week 24. There were no differences in the number of patients who added a new agent among the 4 groups. The datasets provided by the applicant did not specify what new agent was added. Therefore it is not known if there were differences between the groups with respect to the addition of a PI vs NNRTI vs RTI. FDA conducted analyses to evaluate the addition of a new agent on the overall study results. Fifteen (28%) patients in the 300-mg dose group and seven patients (25%) in the placebo group added a new agent prior to week 24. Results for the DAVG $_{24}$ analysis for patients who added or did not add a new agent prior to week 24 are shown below in Table 6.1.3.E.

Table 6.1.3.E. Effect of Treatment Changes on HIV RNA Response

	300 MG N=54	PLACEBO (n=28)
# ADDED NEW AGENT <WK 24	15 (28%)	7 (25%)
OVERALL DAVG24	-0.58	+0.02
DAVG24 ADDED NEW AGENT	-0.33	-0.49
DAVG24 DID NOT ADD NEW AGENT	-0.67	+0.18

These anyalses show that the decline in HIV RNA in the tenofovir 300 mg group was not attributed to the addition of a new agent. Patients who did not add a new agent had a greater reduction in HIV RNA at week 24 versus those who added a new drug. DAVG $_{24}$ results were similar for the overall population and those who did not add a new agent. Also 26% (14/54) patients in the 300 mg group achieved HIV RNA < 400 copies/mL of which only 4 of these patients added a new agent.

HIV RNA Results According to Demographic/Baseline Characteristics

The applicant conducted several subgroup analyses based on age, sex, and race. Statistically significant differences in HIV RNA decreases favoring tenofovir over placebo were observed for each of the age, race and sex subgroups.

Randomization for study 902 was stratified according to baseline HIV RNA (<20,000, ≥ 20,000 copies/mL), baseline CD4 (<200, ≥ 200 cells) and prior antiretroviral therapy (< 4 agents, ≥ 4 agents). Table 6.1.3.F. summarizes the results of the HIV RNA responses by baseline stratification. A statistically significant difference in virologic response for tenofovir 300 mg compared to placebo was not observed in patients with who received < 4 prior antiretroviral agents. However there were numerical differences, comparable to the overall response for these subgroups. For those who received less than 4 drugs prior to enrollment the mean DAVG $_{24}$ was –0.59 and –0.24 for the 300 mg group and placebo group, respectively.

Table 6.1.3.F. HIV RNA Results by Randomization Strata: Mean DAVG $_{24}$ (SD)

Stratum	Tenofovir 300 mg	Placebo	P-value
HIV RNA			
< 20,000 copies/mL	-0.6 (0.66) N=47	-0.05 (0.70) N=22	0.002
≥ 20,000 copies/mL	-0.4 (0.32) N=7	+0.24 (0.67) N=6	0.032
CD4			
< 200 cells/mm^3	-0.24 (0.42) N=15	+0.33 (0.31) N=7	<0.001
≥ 200 cells/mm^3	-0.71 (0.65) N=39	-0.09 (0.76) N=21	0.002
Prior ARV Use			
< 4 ARV	-0.59 (0.61) N=33	-0.24 (0.69) N=17	0.077
≥ 4 ARV	-0.56 (0.67) N=21	+0.41 (0.49) N=11	<0.001

The results noted for this subgroup are somewhat inconsistent with that observed in studies 901, 907 and in the virology substudies in 902 and 907. Historically antiretroviral naïve patients or patients with several treatment options tend to have greater reductions in HIV RNA compared to those who are treatment experienced or have decreased susceptibility to particular drug classes under study. Antiretroviral naïve patients, patients who were either fully susceptible to NRTIs or patients who did not have any zidovudine associated mutations at baseline in studies 901, 902 and 907 had HIV RNA reductions in the range of 0.8 to greater than 1 log $_{10}$ copies. In addition the treatment response for the placebo patients who received < 4 prior antiretroviral agents (DAVG $_{24}$ –0.24) was the largest seen in any placebo subgroup. This result was affected by the addition of new antiretroviral agents. Of the 17 patients who received less than 4 prior antiretroviral agents in the placebo group, 4 added a new antiretroviral prior to week 24. The mean DAVG $_{24}$ for the 4 patients who added a new antiretroviral was –1.26 log $_{10}$ compared to +0.09 log $_{10}$ for the patients who did not add a new agent. Therefore, it appears that this finding may be a result of the addition of new antiretroviral agents in the placebo subgroup rather than a lack of treatment effect of tenofovir in patients who received < 4 prior antiretroviral agents.

In addition, FDA conducted statistical tests to examine interactions between the randomization subgroups for viral load, CD4 cell counts and prior antiretroviral use. These tests explore whether the size of the treatment difference between tenofovir 300 mg and placebo is similar between subgroups. Table 6.3.1.G. summarizes the results of these analyses. Based on an ANOVA (Analysis of Variance) model that included main effects for treatment group, randomization strata and treatment by stratum interaction, no significant interaction was seen for the subgroups based on baseline HIV RNA, CD4 cell counts or prior antiretroviral drug use.

Table 6.3.1.G. HIV RNA Response by Randomization Strata Interaction

Stratum	Tenofovir 300	Placebo	Mean Treatment Effect (TDF-Placebo)	Mean Treatment Effect Difference	p-value* (Treatment by Stratum interaction)
HIV RNA					
< 20,000 copies/mL	-0.6 (0.66) N=47	-0.05 (0.70) N=22	-0.55	0.08	0.482
≥ 20,000 copies/mL	-0.4 (0.32) N=7	+0.24 (0.67) N=6	-0.64		
CD4					
< 200 cells/mm^3	-0.24 (0.42) N=15	+0.33 (0.31) N=7	-0.57	0.05	0.187
≥ 200 cells/mm^3	-0.71 (0.65) N=39	-0.09 (0.76) N=21	-0.62		
Prior ARV Use					
< 4 ARV	-0.59 (0.61) N=33	-0.24 (0.69) N=17	-0.35	0.62	0.384
≥ 4 ARV	-0.56 (0.67) N=21	+0.41 (0.49) N=11	-0.97		

*p-value for treatment by stratum interaction is statistically significant at α=0.15 level of significance.
P-values are calculated based on a ANOVA model

CD4 Cell Count Responses

Mean change and mean DAVG analyses for CD4 cell counts are presented in table 6.1.3.H. The mean changes from baseline were -14 cells/mm^3 for the 300 mg group compared to +20 cells/mm^3 for the placebo group. Differences between treatment groups were not statistically significant.

Table 6.1.3.H: CD4 Cell Count Response

		Tenofovir		
	Placebo (N=28)	75 mg (n=53)	150 mg (n=51)	300 mg (n=54)
Mean Change at week 24	+20	+18	0	-14
Mean Change at week 48	NA	+10	+20	+11
Mean $DAVG_{24}$	-3	+1.8	-11.3	-10.5
Mean $DAVG_{48}$	NA	+8.3	+3.2	-5.6

To further investigate the modest changes in CD4 cell counts observed in this study, FDA conducted subgroup analyses to evaluate CD4 responses by baseline CD4 cell count. A cut off of 200 cells was chosen based on the protocol stratification scheme. Patients with baseline CD4 cell counts < 200 appeared to have a net gain (numerical) in CD4 cell count. However patients with baseline CD4 counts > 200 appear to have a net treatment loss, numerically. This finding is encouraging because CD4 increases in patients with lower cell counts are important for minimizing the risk of opportunistic infections.

Table 6.1.3.I: CD4 Cell Count Response by baseline CD4 (DAVG $_{24}$ and Mean Change)

BASELINE CD4 GROUP	PLACEBO	TENOFOVIR 300 MG	NET TREATMENT EFFECT
DAVG$_{24}$ Results			
< 200 cells/mm^3	-15.5 (n=8)	+14.5 (n=14)	30
> 200 cells/mm^3	+1.1 (n=20)	-19.3 (n=40)	- 20.4
Mean Change Results			
< 200 cells/mm^3	-2.2 (n=8)	+ 12.1 (n=14)	14.3
> 200 cells/mm^3	26.8 (n=20)	-22.7 (n=40)	- 49.5

Efficacy Summary:

In sum, statistically significant reductions in HIV RNA favoring tenofovir 300 mg over placebo were observed. Numerical differences favoring tenofovir over placebo were observed for the < 400 and < 50 copies/mL analyses. No statistically significant differences between placebo and tenofovir 300 mg were seen for changes in CD4 cell counts over 24 weeks.

APPEARS THIS WAY
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6.2 Clinical Trial GS-98-907

"A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Safety and Efficacy of the Tenofovir in Combination With Other Antiretroviral Agents for the Treatment of HIV-1 Infected Patients.

6.2.1. Study Design

Study 907 was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of tenofovir versus placebo when added to stable antiretroviral regimens. Subjects between the ages of 18 and 65 years of age, with plasma HIV-1 RNA levels between 400 and 10,000 copies/mL, and currently receiving a stable antiretroviral regimen for at least 8 weeks were enrolled into the trial. A stable regimen was defined as standard antiretroviral therapy consisting of no more than 4 active agents. Subjects were randomized in a 2:1 ratio to add either tenofovir or placebo to their existing regimen.

Patients were encouraged to continue their baseline regimens, for at least 24 weeks postrandomization. At 24 weeks patients randomized to placebo were offered tenofovir 300 mg for the remainder of the 48 week study.

Study subjects were seen at week, 2, 4, 8, 12, 16, 20, 24, 28, 32, 40, 44, and 48. Adverse events, physical exam, laboratory monitoring for toxicity and immunologic and virologic assessments of efficacy were preformed at regular intervals. Pharmacokinetic, virology and bone density substudies were also conducted.

Adverse Events and laboratory abnormalities were assessed by the standardized ACTG Toxicity Grading Table. Based on the preclinical evidence of nephrotoxicity, patients were permanently discontinued from study drug for a confirmed serum creatinine > 2.0 mg/dL. Patients were also permanently discontinued from study drug for all drug related grade 4 events. There were no criteria for study drug discontinuation due to lack or loss of virologic response.

6.2.3 Analysis Plan

The primary efficacy endpoints were the time-weighted change in $\log_{10}$ HIV RNA at week 24 ($DAVG_{24}$) and mean change from baseline for CD4 cell counts. Secondary endpoints included proportion of patients with HIV RNA < 50 and < 400 copies/mL at weeks 16, 24 and 48, DAVG48, development of resistance and the role that baseline mutations had with regard to antiviral response in a subset of patients, change in RNA and CD4 for placebo cross over patients, time to increase in HIV RNA > 400.

Evaluations of HIV RNA were as follows:

For the US sites, the FDA approved assay, Ultrasensitive HIV-1 Monitor Test (version 1.0), was used at screening and for all post screening values. The Amplicor Test (version 1.0) was used in cases where viral load was > 75,000 copies/mL

For the European/Australian sites, both versions (1.0 and 1.5) of the Ultrasensitive Test were used at screening. Of note the 1.5 version is not FDA approved. Those patients who had a 0.7 log difference between the 1.0 and 1.5 version assays, with the higher RNA on the 1.5 version, were presumed to have non-clade B virus and all subsequent RNA measurements were performed using the 1.5 version assay which detects non-clade B virus. Those patients with < 0.7 log difference continued to have RNA measurements with the 1.0 version assay.

The plan for using 2 RNA assays in the trial was discussed with FDA during the design of the trial. This approach was acceptable to the Division with the thought that pooling data from 2 assays in this case would not impact the overall study results.

The primary and secondary efficacy endpoints were assessed for differences between the two treatment groups. The time-weighted change from baseline was calculated by using the trapezoidal rule with all available post baseline data minus the baseline average. The primary analysis was performed using the ITT and as treated population. The ITT and as treated analyses grouped subjects according to randomized treatment and utilized all follow-up data.

The primary safety endpoint was the incidence of patients with grade 3 or greater adverse events and laboratory abnormalities. The secondary safety endpoints were the proportion of patients who discontinued study drug due to adverse events, time to first study drug dose modification and time to study drug discontinuation and changes in weight and Karnofsky performance status. All patients who received at least 1 dose of study drug were assessed for safety. Treatment-emergent events categorized using COSTART terms were compared between arms. In addition all bone fracture events regardless of cause or severity were evaluated in conjunction with all relevant laboratory data and prior medical histories.

6.2.3. Study Population and Patient Disposition

A total of 552 patients were enrolled and 550 patients received at least 1 dose of study drug. The baseline demographic characteristics were similar for both treatment groups (see Table 6.2.3.A). Patients were predominantly male (85%), Caucasian (69%), median age of 41 years (22-70) with a mean HIV RNA of 3.36 $\log_{10}$ copies/mL and mean CD4 cell count of 427 cells/mm^3. The overall mean duration of prior antiretroviral therapy was 5.4 years. Of note, the mean duration on the current antiretroviral regimen was 3.8 years in the tenofovir group and 3.6 years in the placebo group.

Table 6.2.3.A. Demographics and Baseline Characteristics

	PLACEBO (N=182)	TENOFOVIR (N=386)
Age mean (range)	42 (27-70)	41(22-66)
Sex – male %	160 (88%)	309 (84%)
Race/Ethnicity		
Caucasian	118 (65%)	261 (71%)
African American	34 (19%)	58 (26%)
Asian	0	2 (<1%)
Hispanic	26 (14%)	42 (11%)
Other	4 (2%)	5 (1%)
Baseline HIV Labs – mean		
Log HIV RNA	3.38	3.35
CD4 cell count	447	417
Mean Prior Antiretroviral Use – years	5.3	5.5
Mean Duration of Current ARV regimen - years	3.8	3.6

All patients received at least two antiretrovirals as part of their background therapy at baseline. The majority (69%) of patients received at least 3 drugs as their background. Overall 22% received 4 drugs in their background regimen. Forty-five percent of patients were receiving a PI plus 1 or more RTIs. There were no differences in the number or type of antiretrovirals in the background therapy among the treatment groups

Baseline genotypic data were obtained from 253 of the 274 patients in the virology substudy. Fourteen patients in the tenofovir group and seven patients in the placebo group did not have sufficient PCR product for genotypic analysis. Ninety-four percent, 58%, and 48% of patients had mutations associated with RTIs, PIs and NNRTIs, respectively. The incidence of mutations was similar across all treatment groups. See Review of Clinical Virology Section for further details.

A total of 6% of patients in each study group discontinued randomized therapy prior to week 24. Discontinuations were comparable across treatment groups. Of note, the protocol did not mandate that patients discontinue due to lack of virologic response

After week 24, a total of 538 patients received tenofovir 300 mg. Of these patients, 53 (10%) prematurely discontinued. Twenty-six (5%) of the discontinuations were due to adverse events. As of the safety update, 475 patients (88%) were still receiving tenofovir treatment. Ten patients who completed 24 weeks did not enroll in the long term safety follow up study 910.

The primary reasons for discontinuation are summarized in Table 6.2.3.B.

Table 6.2.3.B. Patient Disposition

	PLACEBO (0-24 WEEKS)	TENOFOVIR 300 MG (0-24 WEEKS)	SAFETY UPDATE: ALL TENOFOVIR
# patients received at least 1 dose of study drug	182	368	538
Prematurely Discontinued	11 (6%)	23 (6%)	53 (10%)
Reasons for Discontinuation			
AE/Intercurrent Illness	5 (3%)	11 (3%)	26 (5%)
Lost to Follow Up	2 (1%)	6 (2%)	7 (1%)
Lack of Virologic Response	1 (<1%)	0	4 (<1%)
Pregnancy	1 (<1%)	1 (<1%)	2 (<1%)
Other	2 (1%)	3 (<1%)	10 (2%)

Source: appendix 12.3.1, table 8 and 9 and table 6-1 page 59-60, Safety Update Table 3-3

Review of Efficacy:

Please refer to Dr. Bhore's statistical review for a comprehensive analysis of the final efficacy results.

The primary efficacy endpoints were the time-weighted change in $\log_{10}$ HIV RNA at week 24 ($DAVG_{24}$) and mean change from baseline for CD4 cell counts. Secondary endpoints included proportion < 400 and < 50 copies/mL. Efficacy results for the HIV RNA endpoints are presented below in Table 6.2.3.C.

Table 6.2.3.C. Summary of Efficacy HIV RNA

	PLACEBO (N=182)	TENOFOVIR 300 MG (N=368)
Mean $DAVG_{24}$	-0.02	-0.61
< 400 copies/mL (week 24)	20/182 (11%)	149/368 (40%)
<50 copies/mL (week 24)	2/182 (1%)	71/368 (19%)

At week 24, there was a statistically significant result favoring tenofovir for the DAVG analysis (-0.61 vs –0.02; p<0.0001). These results are similar to that observed in study 902.
Also significant results were seen favoring tenofovir for the proportion < 400 and < 50 copies/mL analyses. Patients who were < 400 or < 50 copies/mL and added a new antiretroviral prior to week 24 were counted as failures in the analyses.

Changes to background regimens were discouraged in study 907; however, some patients did change their regimen. FDA conducted exploratory analyses to evaluate the impact of the addition of a new agent on the overall study results. The results of these analyses are presented in Table 6.2.3.D. Overall treatment changes did not appear to affect the HIV RNA response. FDA concluded that the decline in HIV RNA in the tenofovir 300 mg groups observed in this study was not attributed to the addition of another drug.

Table 6.2.3.D Effect of Treatment Changes on HIV RNA Response

	PLACEBO (n=182)	TENOFOVIR 300 MG N=368
# ADDED NEW AGENT <WK 24	10 (5.5%)	19 (5.2%)
OVERALL DAVG24	-0.02	-0.61
ADDED NEW AGENT: $DAVG_{24}$	+0.06	-0.29
DID NOT ADD NEW AGENT: $DAVG_{24}$	-0.03	-0.63
OVERALL < 400 COPIES/MI	21 (12%)	154 (42%)
ADDED NEW AGENT: < 400 COPIES/MI	1 (0.5%)	5 (1.4%)
DID NOT ADD NEW AGENT: < 400 COPIES/MI	20 (11%)	149 (40%)
OVERALL < 50 COPIES/MI	2 (1%)	76 (22%)
ADDED NEW AGENT: < 50 COPIES/MI	0 (0%)	5 (1.4%)
DID NOT ADD NEW AGENT: < 50 COPIES/MI	2 (1%)	71 (19.3%)

HIV RNA Results According to Demographic/Baseline Characteristics

The applicant conducted several subgroup analyses based on age, sex, and race. Statistically significant differences in HIV RNA decreases favoring tenofovir over placebo were observed for each of the age, race and sex subgroups.

Randomization for study 907 was stratified according to baseline HIV RNA (<5000, ≥5000 copies/mL), baseline CD4 (<200, ≥ 200 cells) and prior antiretroviral therapy (< 4 agents, ≥ 4 agents). Treatment differences between the 300 mg and placebo groups were significant favoring tenofovir for all randomization strata.

In addition, FDA conducted statistical tests to examine interactions between the randomization subgroups for viral load, CD4 cell counts and prior antiretroviral use. These tests explore whether the size of the treatment difference between tenofovir 300 mg and placebo is similar between subgroups. Results of these analyses are presented in Table 6.2.3.E.

Table 6.2.3.E:
Subgroup Analyses—Viral Load by Randomization Strata Interaction for Study 907 (ITT Population)

	Tenofovir DF 300mg			Placebo			Mean Treatment Effect (TDF-Placebo)	p-value (Treatment by Stratum interaction)
$DAVG_{24}$ Stratum\	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^3	45	-0.39	(0.55)	21	+0.05	(0.37)	**-0.44**	0.230
≥200 cells/mm^3	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 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 α=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.

A statistically significant treatment interaction was observed for the subgroup of patients who received < 4 prior antiretroviral agents vs ≥ 4 prior antiretroviral agents (p-value=0.045 significant at α=0.15 level). These treatment interactions show that patients who received < 4 prior antiretroviral agents had larger net HIV RNA reductions using tenofovir than patients who received ≥ 4 prior antiretroviral agents. Historically patients who are treatment experienced or have decreased susceptibility to particular drug classes under study tend to have smaller reductions in HIV RNA compared to antiretroviral naïve patients or patients who have received limited antiretroviral treatment. This result is not suprising given the fact that patients who received ≥ 4 prior agents had more baseline resistance, specifically thymidine analogue mutations M41L or L210W, compared to patients who received < 4 prior agents. (Please also refer to section 9.0 Review of Clinical Virology). Of the tenofovir treated patients with baseline genotype available and who received < 4 prior agents, 12% had the M41L or L210W mutation present at baseline compared to 41% of patients who received ≥ 4 prior agents.

No significant interaction was seen for the subgroups based on baseline HIV RNA or CD4 cell counts. The net benefit in reduction of viral load due to tenofovir was similar in patients who had either < 5,000 copies/mL or ≥ 5,000 copies/mL and < 200 or ≥ 200 cells/mm^3 at baseline.

CD4 Cell Count Responses

CD4 cell count changes are presented in table 6.2.3.F. A statistically significant difference in the $DAVG_{24}$ for CD4 favoring tenofovir was observed. The mean $DAVG_{24}$ was +12 cells/mm^3 in the tenofovir group compared to –10 cells/mm^3 in the placebo group, resulting in a net treatment difference of approximately 20 cells/mm^3. For the change from baseline in CD4 cell counts, a statistically significant difference favoring tenofovir was seen at every time point except week 24.

Table 6.2.3.F: FDA Analyses: CD4 Cell Count Response

	Placebo (N=182)	Tenofovir 300 mg (n=368)
Mean $DAVG_{24}$	-10	12.6
Mean Change	-4.9	11.6

CD4 cell count changes were modest for the 300 mg dose group. Again, this may be explained by the inherent design of the trial in that for patients with relatively stable CD4 cell counts, the addition of one new drug is not necessarily expected to further increase CD4 cell counts over 24 weeks. As in study 902, analyses based on baseline CD4 cell counts were also conducted. The results are presented in Table 6.2.3.G.

Table 6.2.3.G: CD4 Cell Count Response by Baseline CD4

Baseline CD4 group	**Placebo (N=182)**	**Tenofovir 300 mg (N=368)**	**Net Treatment Effect**
$DAVG_{24}$ Results			
< 200 cells/mm^3	-3.1 (n=21)	+22.2 (n=45)	+25.3
≥ 200 cells/mm^3	-11.5 (n=161)	+11.3 (n=323)	+22.8
Mean Change Results			
< 200 cells/mm^3	-0.3 (n=21)	42 (n=45)	42.3
≥ 200 cells/mm^3	-3.6 (n=161)	7.3 (n=323)	10.9

Increases in CD4 cell counts were noted over 24 weeks in patients with CD4 cell counts < 200. Again, this finding is encouraging because CD4 increases in patients with lower cell counts are important for minimizing the risk of opportunistic infections.

Efficacy Summary:

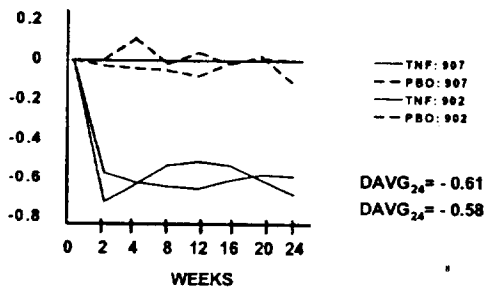
In sum, statistically significant differences in HIV RNA favoring tenofovir were seen for the $DAVG_{24}$ and proportion < 400 and < 50 copies/mL analyses. A statistically significant treatment effect was noted for the prior antiretroviral use randomization strata. Tenofovir treated patients with ≥ 5,000 copies/mL at baseline or patients who received ≥ 4 prior antiretroviral agents had a smaller net HIV RNA reduction at week 24 compared to patients with < 5,000 copies/mL or patients who received < 4 prior antiretroviral agents at baseline.
Statistically significant changes in CD4 cell counts favoring tenofovir were noted at week 24 for the $DAVG_{24}$ analyses. For the change from baseline in CD4 cell counts, a statistically significant difference favoring tenofovir was seen at every time point except week 24.

7.0 Integrated Review of Efficacy

The antiviral activity of tenofovir DF was evaluated in 3 studies ranging from 35 days to 48 weeks. All studies showed decreases in HIV RNA over the protocol specified time points. In studies 901 and 902, decreases in HIV RNA were greater in the 300 mg group compared to 75 mg and 150 mg groups. No differences in decreases in HIV RNA were noted between tenofovir 300 and 600 mg. Therefore 300 mg was chosen for further study and proposed as the marketed dose.

In the two pivotal studies (902 and 907), statistically significant differences were noted for the primary efficacy endpoint, $DAVG_{24}$, favoring the tenofovir groups over placebo. Figure 1 displays the mean change from baseline for HIV RNA for studies 902 and 907. Mean reductions in HIV RNA were similar for both studies 902 and 907. Also, in study 902, decreases in HIV RNA were sustained over 48 weeks for all dose groups (75, 150 and 300 mg).

Figure 1: Mean Change From Baseline: HIV RNA



For the proportion < 400 and < 50 copies/mL analyses, numerical differences favoring tenofovir were observed in study 902. At week 24 the proportion < 400 was 19% for tenofovir 300 mg vs 7% for placebo. No patients in the placebo group and 11% of patients in the tenofovir group achieved HIV RNA < 50 copies at week 24. In study 907, a greater proportion of patients in the tenofovir group achieved HIV RNA < 400 copies/mL compared to placebo. At week 24 the proportion < 400 was 40% for the tenofovir group vs 11% for the placebo group. One percent of patients in the placebo group and 20% of patients in the tenofovir achieved HIV RNA < 50 copies at week 24

In study 902, no statistically significant difference between tenofovir and placebo for CD4 cell counts at any timepoint was noted. A decrease of 14 cells was noted for the 300 mg group compared to an increase of 20 cells in the placebo group at week 24. By week 48, the mean change from baseline for CD4 cell counts increased to 11 cells. In study 907, statistically significant changes in CD4 cell counts favoring tenofovir were noted at week 24 for the $DAVG_{24}$ analyses. In addition, for the mean change from baseline in CD4 cell counts analysis, a statistically significant difference favoring tenofovir was seen at every time point except week 24.

For both studies increases in CD4 cell counts were modest; approximately 11 cells in study 907 at week 24 and 11 cells in study 902 at week 48. However, similar results were reported for the abacavir study (CNA2003). This study was similar in design to the tenofovir studies 902 and 907. The activity of abacavir versus placebo when added to stable antiretroviral regimens was evaluated in treatment experienced patients. No statistically significant differences for change in CD4 from baseline was noted between abacavir and placebo; however there was a trend in favor of the abacavir group (+30 vs +1 cells/mm^3). Results from the CNA2003, 902 and 907 studies suggest that small changes in CD4 cell counts can be expected in treatment experienced patients

following the addition of one new agent to a stable background antiretroviral regimen. Perhaps this is not the optimal study design to assess changes in CD4 cell counts for treatment experienced patients. Evaluation of CD4 cell counts in other studies and in patients with lower baseline CD4 cell counts are needed.

Overall, the antiviral activity of tenofovir has been demonstrated in two pivotal studies. Mean reductions in HIV RNA were similar for both studies 902 and 907. In both studies statistically significant differences of approximately 0.5 to 0.6 log reductions were observed. For the < 400 and < 50 analyses, numerical differences favoring tenofovir were seen in study 902 and statistically significant differences favoring tenofovir were seen in study 907. Modest increases in CD4 cell counts were observed for tenofovir compared to placebo in study 907, whereas, no differences in CD4 cell counts changes between tenofovir and placebo were seen in study 902 over 24 weeks. It is also important to note that the study populations in studies 902 and 907 may not have been optimal for observing large increases in CD4 cell counts, given the fact that only one new drug was added to a stable background regimen. The addition of one new agent did not produce substantial increases in CD4 cell counts over time. Therefore further evaluations of CD4 cell counts in studies with different designs are needed.

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8.0 Summary of Supportive Trials

8.1 Study GS-99-908

"An open-Label, Multicenter, Compassionate Access Study of the Safety of Tenofovir DF Administered In Combination with Other Antiretroviral Agents for the Treatment of HIV-1 Infected Patients"

8.1.1 Study Design:

Study 908 was an open label single arm study to evaluate the safety of tenofovir 300 mg in patients who had limited treatment options. Subjects greater than 18 years of age with plasma HIV RNA $\geq$ 10,000 copies/mL and CD4 counts $\leq$ 50 cells/mm^3 were enrolled into the trial. Patients either added tenofovir to their current, stable regimen or constructed a new antiretroviral regimen.

Patients were monitored for safety using periodic physical exams and medical assessments including collection of adverse event reports and measurements of vital signs and serial laboratory tests.

8.1.2 Study Population and Patient Disposition

A total of 296 patients were enrolled and 291 patients received at least 1 dose of study drug. The demographic and baseline characteristics are summarized in table 8.1.2.A. Patients were predominantly male (93%), Caucasian (70%), mean age of 42 years with a mean HIV RNA and CD4 cell count of 4.87 log copies/mL and 36 cells/ mm^3 at baseline respectively. Ninety-three percent of patients had one or more AIDS defining conditions at baseline. Over 95% of patients previously received lamivudine, zidovudine or stavudine. Ninety-three percent of patients received lopinavir/ritonavir during the study. The median follow up on study was 49 weeks.

Table 8.1.2.A. Demographics and Baseline Characteristics

	Tenofovir (n=291)
Age mean (range)	42 (18-65)
Sex – male %	270 (93%)
Race/Ethnicity	
Caucasian	203 (70%)
African American	45 (16%)
Hispanic	34 (12%)
Asian/Pacific Islander	5 (2%)
Native American	2 (< 1%)
Other	0 (<1%)
Baseline HIV Labs – mean	
Log HIV RNA	4.87
CD4 cell count	39

Through the safety cut off, 34% of patients prematurely discontinued study drug. Nine percent of the discontinuations were due to adverse events. The primary reasons for discontinuation is summarized below in table 8.1.2.B. This table includes data through the safety cut off date.

Table 8.1.2.B. Patient Disposition: 908

	Original NDA
# Patients Enrolled	296
# patients received 1 dose of study medication	291
Prematurely Discontinued	100 (34%)
AE/Intercurrent Illness	27 (9%)
Other	19 (6%)
Death	16 (5%)#
Lost to Follow Up	11 (4%)
Lack of Virologic Response	14 (5%)
Patient Noncompliance	9 (3%)
Prohibited Concomitant Medication	4 (1%)

Source ISS table 9-1, vol 78 Table 6-1 and Table 8-4
Note a total of 24 deaths occurred in the study; however 8 deaths occurred after study drug discontinuation. These patients have other reasons cited for study discontinuation

Overall the adverse events and laboratory abnormalities reported during the trial is consistent with that observed in studies 902 and 907 and with those expected in a study population of advanced AIDS patients. Summary information for selected adverse events and laboratory abnormalities, serious adverse events and deaths are summarized in the ISS.

8.2 Study 701:

Study 701 was a randomized, double-blind, placebo controlled trial to evaluate the safety, activity and pharmacokinetics of single and multiple doses of IV tenofovir in patients with CD4 counts $\geq$ 200. Four dose levels were planned; 1, 3, 6 and 10 mg/kg. Only the first two dose levels were completed. An oral prodrug formulation became available and development of the IV formulation was abandoned. A single IV infusion of tenofovir vs placebo was given on Day 1, followed by a one week observation period. Patients who tolerated the single dose received daily IV infusion for 7 days. HIV RNA responses were evaluated for 4 weeks after the last dose. A total of 20 patients were enrolled into this study (16 active; 4 placebo). The majority of patients were male (85%) and Caucasian (60%). The mean baseline viral load and CD4 cell count was 4.65 $\log_{10}$ and 450 cells/mm^3, respectively. Twenty five percent of patients were treatment experienced. At study day 14 (7 days of multiple dosing), mean (median) HIV RNA decrease for the 1 and 3 mg/kg dose groups were 0.72 $\log_{10}$ (0.86 $\log_{10}$) and 0.6 $\log_{10}$ (1.1 $\log_{10}$), respectively. Mean change from baseline at day 14 was an increase of 47 and 31 cells for the 1 mg/kg and 3 mg/kg dose groups. Mean change in viral load and CD4 cell counts was+0.13 $\log_{10}$ and −76 cells, respectively for the placebo group.

8.3 Study 901

Study 901 was a randomized, double-blind, placebo controlled trial to evaluate the safety, activity and pharmacokinetics of oral tenofovir at doses of 75, 150, 300 or 600 mg once daily. Fifty nine patients with CD4 counts $\geq$ 200 and HIV RNA $\geq$ 10, 000 copies/mL were enrolled into one of 7 cohorts:

- tenofovir 75 mg QD
- tenofovir 150 mg QD
- tenofovir 300 mg QD
- tenofovir 600 mg QD
- placebo QD
- tenofovir 75 mg QD + hydroxyurea 500 mg bid
- placebo QD + hydroxyurea 500 mg bid

A total of 46 patients received one of the 4 doses of tenofovir and 11 patients received placebo. Patients received a single dose of study drug on day 1 followed by a one week observation period. Patients who tolerated the single dose of study drug entered the multiple dose phase and received study drug once daily for 28 days. Patients in the tenofovir 75 mg + hydroxyurea cohort were eligible to continue for up to 12 months. At this time patients were encouraged to add other antiretrovirals to their regimen. A 12 month open label extension phase was also available to patients who completed 12 months of tenofovir 75 mg + hydroxyurea or tenofovir 600 mg. The majority of patients in this study were male (83%). Equal proportions of Caucasian and black patients were enrolled. Sixty six percent of patients were antiretroviral experienced. Mean baseline viral load and CD4 cell counts were 4.63 $\log_{10}$ and 356 cells/mm^3, respectively.

Statistically significant differences were noted for all the tenofovir groups compared to placebo for changes in HIV RNA. The mean change from baseline at day 35 was +0.03, -0.33, -0.51, -0.83 and –0.84 for the placebo, 75, 150, 300 and 600 mg groups, respectively. Results were similar for the 75 mg and 75 mg + hydroxyurea group. RNA decreases were greater in the 300 and 600 mg groups compared to 75 and 150 mg. Similar HIV RNA responses were noted for the 300 and 600 mg groups. No significant differences were noted between groups for CD4 counts. At day 35 increases in CD4 cell counts were noted for all groups, +74, +7, +49, +7 and +64 for the placebo, 75, 150, 300 and 600 mg groups respectively. The increases in CD4 cell counts seen in this study were widely variable due to the small sample size.

9.0 Review of Clinical Virology

9.1 Objectives:

The objectives of the genotypic and phenotypic substudies in studies 902 and 907 were the following:

- Characterize HIV RT mutations that develop during tenofovir therapy through genotypic analysis of plasma HIV
- Determine whether phenotypic resistance to tenofovir occurs after 24 or 48 weeks of tenofovir therapy
- Determine whether RT mutations at baseline affect the response to tenofovir therapy
- Specifically address the potential effects of ZDV and 3TC resistance mutations, either alone or in combination, on response to tenofovir therapy.

9.2 Analysis Plan:

Genotype:

The applicant prospectively defined the following four baseline mutation groups; (1) No Zidovudine-associated mutations, wild-type 184, (2) Zidovudine-associated mutations, wild-type 184, (3), No Zidovudine-associated mutations, M184V/I, and (4) Zidovudine-associated mutations, M184V/I. Zidovudine-associated mutations were defined as M41L, D67N, K70R, L210W, T2215Y/F or K219Q/E/N. The protocol specified analysis utilized the intent to treat population and as treated population. The primary study endpoint, $DAVG_{24}$, was also used in the virology substudy. $DAVG_{24}$ was calculated for both treatment groups by the baseline mutation groups cited above.

Secondary analyses of patients with the following mutation patterns at baseline were also conducted.

- Wild type 215, wild type 184
- T215Y/F, wild type 184
- Wild type 215, M184V/I
- T215Y/F, M184V/I
- L74V/I
- K65R
- T69D/N
- Q151M
- T69 insertion mutations
- Any primary NNRTI-associated resistance mutation, per the Resistance Collaborative Data Analysis Plan
- Any primary PI associated resistance mutation, per the Resistance Collaborative Data Analysis Plan

Also the development of nucleoside associated mutations, K65R RT mutation, and other RT and PI mutations during the study were be compared between the tenofovir and placebo groups to determine if tenofovir treatment affects the development of these mutations.

Phenotype

Development of reduced susceptibility to tenofovir and baseline susceptibility of plasma HIV to tenofovir was assessed by the applicant. The applicant also determined the following for patients with a $\geq$ 4 fold increase in IC_{50} for tenofovir with respect to baseline IC_{50} at any post-baseline timepoint:

- HIV genotypic changes corresponding to observed phenotypic changes;
- potential phenotypic cross resistance to other approved antiretroviral agents;
- Correlation with HIV RNA changes

A 4 fold or greater cut off was used because [redacted] determined that this threshold is an indictor of potential resistance in their assay.

Baseline tenofovir susceptibility was also correlated with baseline genotype and response to tenofovir treatment. A linear regression analyses was used to compare the absolute baseline tenofovir susceptibility to change in HIV RNA at week 24.

9.3 Studies 902 and 907

9.3.1. Background and Patient Disposition:

9.3.1.1. Genotype:

A prospective, randomized virology substudy was conducted in studies 902 and 907.

In study 902, baseline genotype data was performed on all patients. Data provided for review included 26 placebo patients and 54 patients treated with tenofovir 300 mg. Data from the 75 mg and 150 mg group was not provided by the applicant. [redacted] conducted the genotypic analyses for baseline, week 24, 48 or early termination HIV samples > 50 copies/mL. The genotypic analyses included amino acids 1-250 of the HIV reverse transcriptase and all of the HIV protease. Ninety-four percent, 57% and 32% expressed RT, PI and NNRTI associated mutations at baseline. The incidence of baseline mutations was similar for both the placebo and tenofovir 300 mg group. Baseline and week 24 genotype data was available for 22 placebo patients and 35 tenofovir patients. Baseline and week 48 genotype data was also available for 37 tenofovir patients.

In study 907 a total of 274 patients were included in the substudy. A 2:1 randomization scheme for tenofovir vs placebo treated subjects was also used in this substudy. [redacted] conducted the genotypic analyses for baseline, week 24 or early termination HIV samples with > 50 copies/mL. Samples that failed to generate genotypic results by [redacted] were then sent to [redacted] The genotypic analyses included amino acids 1-400 of the HIV reverse transcriptase and all of the HIV protease. Baseline genotype was obtained from 253 (92%) of the 274 patients. Fourteen and seven patients in the tenofovir and placebo groups respectively, failed to generate sufficient PCR product for analysis. Therefore baseline data was available for 169 patients in the tenofovir group and 84 patients in the placebo group. Ninety-four percent, 58%, and 48% of patients had mutations associated with RTIs, PIs and NNRTIs, respectively. The incidence of mutations was similar for both treatment groups. Also there were no significant differences between the two groups with regard to baseline antiretroviral usage. No differences were noted between patients in the virology substudy and all patients enrolled in the trial. Baseline and week 24 genotype data was available for 93 and 70 patients from the tenofovir and placebo groups respectively. Reasons for missing week 24 genotype data include, no PCR product, HIV RNA < 50 copies/mL or no sample.

Although 2 different assays were used in study 902 and 907, both the Division and the applicant concluded that these assays were similar and pooling of data was acceptable. For both studies combined genotypic data was available for 110 and 222 patients in the placebo and tenofovir 300 mg groups, respectively.

9.3.1.2 Phenotype:

902:

Baseline phenotype as determined by the [redacted] assay was available for 44 patients in the tenofovir 300 mg group. Baseline phenotype was not provided for the placebo, 75 mg or 150 mg group. Additional analyses were conducted with the [redacted] assay or by recombinant virus assays at Gilead Sciences. This data was not used in the pooled 902 and 907 analysis. Only data by the [redacted] assay in both studies were pooled.

907:

One hundred and thirty seven patients were randomly assigned into the virology phenotype study. Phenotypic results were available for 85 patients; 56 in the tenofovir groups and 29 placebo patients. No baseline differences were noted for either group. The mean baseline susceptibility to tenofovir and the other approved NRTIs were similar for both treatment groups.

9.4 Results:

9.4.1. Baseline Genotype:

Studies 902 and 907 included analysis plans to prospectively evaluate HIV RNA response according to the presence of baseline mutations. Table 9.4.1.A and B summarizes FDA analyses of virologic response for the protocol specified baseline mutation groups. These analyses incorporated pooled data from studies 902 and 907. As shown in Table 9.4.1.A. decreases in HIV RNA were observed in tenofovir treated patients with baseline zidovudine-associated mutations or M184V. Statistically significant decreases in HIV RNA were also noted in tenofovir treated patients with baseline NNRTI and PI associated mutations, T215Y/F, T69D/N, and L74V/I compared to placebo.

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Table 9.4.1.B. RNA Responses by Baseline Resistance Mutations (ITT) [A]

Baseline Mutation Group	Mean $DAVG_{24}$ (n)		Net Treatment Effect
	Placebo	Tenofovir	
All Patients	-0.03 (110)	-0.59 (222)	-0.56
No M184V/No ZDV-R[1]	-0.08 (9)	-0.31 (17)	-0.23
M184V / No ZDV-R[1]	-0.12 (20)	-0.96 (51)	-0.84
No M184V	+0.08 (40)	-0.42 (73)	-0.50
M184V	-0.08 (70)	-0.67 (149)	-0.59
No ZDV-R[1]	-0.11 (29)	-0.80 (68)	-0.69
ZDV-R[1]	0.00 (81)	-0.50 (154)	-0.50
ZDV-R[1]/ No M184V	+0.13 (3)	-0.45 (56)	-0.58
ZDV-R[1] + M184V	-0.08 (50)	-0.52 (98)	-0.44
T215Y/F	+0.03 (53)	-0.35 (106)	-0.38
T215Y/F / No M184V	+0.14 (24)	-0.37 (44)	-0.51
T215Y/F + M184V	-0.06 (29)	-0.34 (62)	-0.28
T69D/N	-0.08 (19)	-0.48 (25)	-0.56
L74V/I	+0.11 (16)	-0.17 (18)	-0.28
K65R	(0)	-0.01 (6)	NA
Q151M	+0.05 (2)	+0.38 (2)	+0.33
T69S Insertions	(0)	+0.29 (2)	NA
NNRTI-R[2]	+0.06 (53)	-0.50 (97)	-0.56
PI-R[3]	0 (70)	-0.52 (129)	-0.52

[A]Patients included in these subgroups may have other zidovudine-associated mutations or mutations in addition to the baseline zidovudine-associated mutations listed

[1]ZDV-R=M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N (Also known as Zidovudine-associated mutations)

[2]NNRTI-R = K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190A/S/E or P263L

[3]PI-R = D30N, V32I, G48V, I50V, V82A/F/T/S, I84V or L90M

Results from the protocol specified analyses are displayed in Table 9.4.1.B. The net reduction in viral load is statistically significant favoring tenofovir over placebo for groups 2, 3, and 4. However a statistically significant result is not observed for group 1. The net mean reduction in HIV RNA was numerically in favor of tenofovir (-0.23). This result may be due to the small sample size. Also several patients in the tenofovir group had the L74V/I or K65R mutation at baseline. The presence of these mutations was shown to reduce tenofovir efficacy.

In the absence of zidovudine-associated mutations (groups 1 and 3), patients with the M184V mutation showed a -0.84 $\log_{10}$ copies/mL decrease in their HIV RNA as compared to -0.23 $\log_{10}$ copies/mL decrease in HIV RNA for patients with wild-type 184, relative to placebo. In the presence of zidovudine-associated mutations (groups 2 and 4), the M184V mutation did not affect the mean HIV RNA responses to VIREAD treatment. Tenofovir treated patients with M184V and zidovudine-associated mutations had slightly greater HIV RNA decreases compared to patients with zidovudine-associated mutations and no M184V ($DAVG_{24}$ –0.52 vs –0.45 $\log_{10}$). However, when considering the effect of placebo, the net treatment effects in these groups were similar (-0.58 vs –0.45 $\log_{10}$). These data suggest a lack of cross resistance between tenofovir and the lamivudine/ abacavir-associated M184V mutation.

Table 9.4.1.B. Protocol Specified Analyses:
RNA Responses by Baseline Resistance Mutations (ITT)[A]

Baseline Mutation Group	Mean $DAVG_{24}$ (n)		Net Treatment Effect	P-value
	Placebo	Tenofovir		
Group 1: (No Zidovudine-associated mutations[1] and Wild type 184)	-0.08 (9)	-0.32 (17)	-0.23	0.321
Group 2: Zidovudine-associated mutations[1] and Wild Type 184	+0.13 (31)	-0.45 (56)	-0.58	<0.001*
Group 3: No Zidovudine-associated mutations[1] and M184V	-0.12 (20)	-0.96 (51)	-0.84	<0.001*
Group 4: Zidovudine-associated mutations[1] and M184V	-0.07 (50)	-0.52 (98)	-0.45	<0.001*

*Statistically significant at 0.05 level of significance
[A]Patients included in these subgroups may have other Zidovudine-associated mutations or mutations in addition to the baseline zidovudine-associated mutations listed
[1]zidovudine-associated mutations =M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N

In addition to the protocol-specified analyses evaluating the impact of baseline mutations on virologic response, FDA conducted several additional exploratory analyses to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Results of these analyses are presented in Table 9.4.1.C. Because of the large number of potential comparisons, statistical testing was not conducted. Descriptions of numerical differences are presented below.

Table 9.4.1.C: HIV RNA Response by Baseline Zidovudine-associated mutations

Baseline Zidovudine-associated mutations[1]	Mean $DAVG_{24}$ (N)			
	MUTATION PRESENT		MUTATION ABSENT	
	Tenofovir	Placebo	Tenofovir	Placebo
Any	-0.50 (154)	0 (81)	-0.80 (68)	-0.11 (29)
M41L	-0.26 (81)	+0.06 (40)	-0.78 (141)	-0.07 (70)
D67N	-0.53 (79)	-0.03 (43)	-0.62 (143)	-0.02 (67)
K70R	-0.71 (67)	-0.03 (40)	-0.54 (155)	-0.02 (70)
L210W	-0.17 (46)	+0.06 (22)	-0.70 (176)	-0.05 (88)
T215Y/F	-0.35 (106)	+0.03 (53)	-0.80 (116)	-0.07 (57)
K219Q/E/N	-0.60 (57)	+0.11 (27)	-0.58 (165)	-0.07 (83)

[1]Patients included in these subgroups may have other zidovudine-associated mutations or mutations in addition to the baseline zidovudine-associated mutations listed

Mean virologic responses were slightly greater among patients without any zidovudine-associated mutations compared to those with at least one zidovudine-associated mutation. As seen in Table 9.4.1.c and in Figure 3 below, the presence of the D67N, K70R or K219Q/E/N mutation alone or in combination with other mutations at baseline did not affect response to tenofovir. In fact response rates were similar regardless if these mutations were present or absent at baseline. Whereas in Figure 4, the activity of tenofovir appears to be diminished in patients expressing the M41L, L210W or T215Y/F mutation at baseline compared to patients who did not have these mutations at baseline. Tenofovir associated decreases in HIV RNA were approximately 0.5 log less when these mutations were present compared to when they were absent at baseline.

Figure 3: HIV RNA Response by Baseline Zidovudine-Associated Mutations

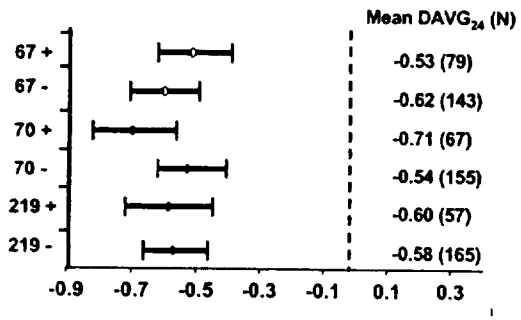
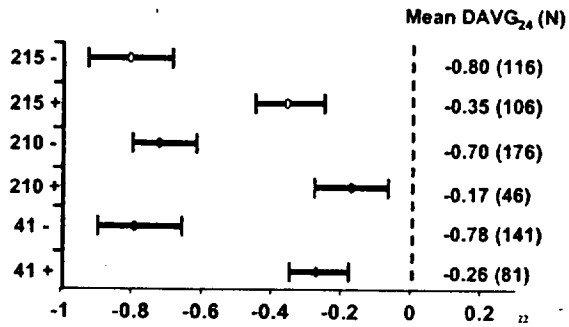


Figure 4: HIV RNA Response by Baseline Zidovudine-Associated Mutations



Subsequently several additional exploratory analyses were then conducted to further investigate the impact of the T215Y/F, M41L and L210 mutations on response . Table 9.4.1.D and Figure 5 show the results from these analyses. Although the above analysis showed a diminished response in tenofovir treated patients expressing the T215Y/F mutation at baseline it was found that this mutation might not have directly affected the activity of tenofovir. The diminished response noted in patients expressing the T215Y/F mutation at baseline appears to be due to the presence of the M41L or L210W mutation and not the T215Y/F mutation. Patients expressing the T215Y/F mutation at baseline without the M41L or L210W mutation had a –0.70 $\log_{10}$ decrease through week 24 compared to a –0.25 $\log_{10}$ decrease if the T215Y/F mutation was present with the M41L or L210W mutation. Additional supportive evidence that the T215Y/F mutation does not affect HIV RNA response is seen in patients with the T215Y/F mutation alone and in patients with T215Y/F mutation in addition to the D67D, K70R and K219Q/E/N. HIV RNA responses for these patients appeared to be unaffected by the T215Y/F mutation, in fact responses were similar to that of the entire group.