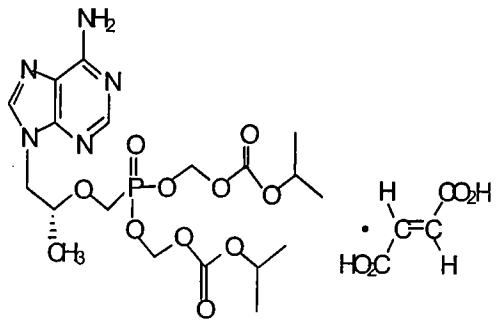
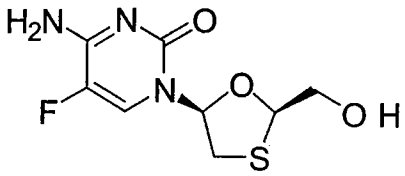
Structural formula:





TENOFOVIR DISOPROXIL FUMARATE **EMTRICITABINE**

Dosage form/route of administration: Tablets/Oral (300mg tenofovir disoproxil fumarate/200 mg emtricitabine)

Indication: Treatment of HIV-1 infection

Related documents: NDAs: 21-356 and 21-500; INDs 53971, 67671, 52849; [redacted]; DMFs [redacted]

Background: Truvada™ is a fixed dose tablet formulation combination product consisting of two active pharmaceutical ingredients, tenofovir disoproxil fumarate (300 mg) *i.e.*, Viread®, and emtricitabine (200 mg) *i.e.*, Emtriva™. Viread® (NDA# 21-356) was approved on October 10, 2001 and Emtriva™ (NDA# 21-500) was approved on July 2, 2003. The approvals of both of these nucleoside analogue reverse transcriptase inhibitors (NRTIs) for HIV-1 were based on the analysis of plasma HIV-1 RNA and $CD4^+$ cell counts in controlled clinical studies. Gilead Sciences, Inc. the sponsor of this combination drug product is seeking the indication of Truvada™ in combination with other approved antiretroviral agents (such as nonnucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infected adults. The recommended dose of Truvada™ is one tablet once daily taken orally. FDA is evaluating the submission under the Accelerated Approval of New Drugs for Serious or Life-threatening Illness (21 CFR 314.510).

The sponsor submitted this application by following the Common Technical Document format. The microbiology information in the Common Technical Document is distributed among different Volumes in all of the five Modules. However, the primary

nonclinical microbiology data are in Volumes 1 of Module 1 and in Volume 1 of Module 4. The clinical microbiology data are in Volumes 10 to 13 of Module 5. Draft microbiology package inset is in Volume 1 of Module 1 and microbiology-related references cited are in Volumes 17 to 20 of Module 5.

Primary microbiology reviews and evaluations of the individual components (Tenofovir disoproxil fumarate, NDA# 21-356 and emtricitabine NDA# 21-500) of the combination product have been extensively reviewed and are not repeated here. The current microbiology review of the fixed dose combination product, Truvada™, evaluates the activity of these drugs tested in combination. The review and analysis include: (1) *in vitro* combination antiviral activity of tenofovir and emtricitabine (2) *in vitro* emergence of resistance (3) emergence of resistance in clinical studies (4) conclusions of the drug combination, and (5) evaluation and revisions to the microbiology portion of the package insert.

Summary: *In vitro* combination studies with FTC and Tenofovir: To determine the combination antiviral activity of emtricitabine (FTC) and tenofovir (TNV) the applicant conducted *in vitro* studies using the combination of these two drugs. The test system involved MT-2 cells infected with laboratory adapted HIV-1_{LAI} strain and a recombinant HIV-1 clinical isolate. Antiviral activity was determined using

MT-2 cells infected with HIV-1 at a multiplicity of infection of 0.03 were seeded onto 96 well plates containing the appropriate concentrations of the test compounds. Uninfected cells run in parallel served as negative controls to evaluate the extent of inhibition and for cytotoxicity. After 5 days of incubation at 37^0C, the antiviral activity of the combined drugs was determined using the – assay. Results of the study showed that the combination of emtricitabine and tenofovir was synergistic with respect to the inhibition of HIV-1 replication.

In support of the synergistic antiviral activity of TNV and FTC, Gilead conducted another set of *in vitro* experiments to determine the extent of intracellular phosphorylation of TNV and FTC to their active metabolites, TNV-diphosphate and FTC-triphosphate, respectively. Results of the study showed that the intracellular phosphorylation of both TNV and FTC to their respective activated metabolites (TNV-diphosphate and FTC-

triphosphate) was unaffected by the simultaneous presence of the other NRTI. This result is consistent with the expectation that the intracellular anabolic activation pathways between TNV (an adenosine analogue) and FTC (a cytidine analogue) would be unaffected in the simultaneous presence of the other. The result also is consistent with the synergistic anti-HIV-1 activity of the combination of TNV and FTC.

In a 5 day *in vitro* combination activity study, the antiviral effect of the combination of TNV and FTC is synergistic. However, in >5 day studies, the FTC-associated resistance mutation at codon 184 in RT gene emerges resulting in the M184I/V amino acid substitution and as a consequence, there was a >100-fold decreases in susceptibility to FTC. Therefore, for the combination of these 2 drugs after >5 days, only tenofovir is expected to be active and it is unlikely that the combination activity will be synergistic. The conclusion from these combined observations is that the drug combination would be synergistic during short term exposure but the synergistic antiviral effect is unlikely during chronic exposure to the drug combination. Thus, the synergistic antiviral effects of the combination of TNV and FTC observed in short term experiments should not be interpreted to indicate that this combination would exert synergistic or additive effect over a longer period of time either or both *in vitro* and/or *in vivo*.

***In vitro* resistance**: According to Gilead, experiments designed for the *in vitro* selection of resistance in HIV-1 with the combination use of TNV and FTC are in progress, but the sponsor submitted available data as an interim report. Resistance selection experiments were initiated by using conventional procedures of sequential passaging of HIV-1 in increasing concentrations of each drug and their combination. The host cell-virus infection systems used were MT-2 cells infected with wild-type strain HIV-1_{IIIb}. Syncytium formation was used as a marker for monitoring virus growth. Genotypic changes in the HIV-1 RNA were analyzed by DNA sequence analysis. In these studies HIV-1 RNA was extracted from virus grown in increasing concentration of the drugs in combination and the DNA sequence of the RT-PCR products determined. The RT sequence corresponding to amino acids 1-250 was determined and compared to that of HIV-1_{IIIb}.

The emtricitabine-resistant M184I mutation in RT gene emerged in 2-3 passages (by 2-3 weeks in culture) in both the FTC alone culture and in the FTC+TNV combination. With continued passage in increasing concentrations of FTC, an M184V mutation developed with more than >100-fold decrease in susceptibility to FTC. The result indicates that under conditions of continued viral replication either in the presence of FTC alone or in combination with TNV and FTC, the emergence of resistance to FTC was not hindered. Thus, TNV does not suppress the emergence of FTC resistance mutation, therefore in this 2-drug combination shortly after exposure only TNV would exert antiviral activity.

With regard to tenofovir, there were no changes at the tenofovir-associated position K65 in the RT after 48 days in culture with increasing concentrations of up to 16-fold the IC_{50} value of TNV, either with TNV alone or in combination of TNV+FTC. In other studies, Gilead reported that by 8 passages of the virus in increasing concentration of tenofovir, mutations at codon 65 in the viral RT gene associated with tenofovir resistance emerged with a 4-fold decrease in susceptibility. In addition, the tenofovir resistant K65R mutation confers an 8-fold decrease in susceptibility to FTC. Thus, when the combination of TNV and FTC are used to inhibit HIV-1 replication, the FTC resistance conferring mutation that emerges rapidly renders FTC inactive, leaving TNV alone to exert antiviral effect, and in course of time the TNV conferring mutation emerges rendering TNV also ineffective. Moreover, the TNV resistance mutation at codon 65 of the RT is also expected to confer additional cross-resistance to FTC. These results suggest that under conditions of continued viral replication *in vivo*, the combination of tenofovir and emtricitabine would select for the M184I/V mutation first and then select for tenofovir resistance in a stepwise fashion.

Resistance in clinical studies: Clinical study GS-01-934: This is an ongoing Phase 3, randomized open label, parallel, active-controlled, multicenter (80 centers in the US and Europe) study of the treatment of antiretroviral naïve HIV-1 infected subjects comparing tenofovir disoproxyl fumarate and emtricitabine administered OAD in combination with efavirenz versus combivir (zidovudine/lamivudine) administered OAD and efavirenz. Five hundred HIV-1 infected subjects with plasma HIV-1 RNA levels >10,000 copies/ml at study entry were randomized 1:1 to one of the two treatment arms. Subjects were stratified on the basis of screening for $CD4^+$ cell count (< or >200 cells/mm^3).

The primary objective of the study is to assess non-inferiority of tenofovir disoproxyl fumarate (TDF) and emtricitabine in combination with efavirenz in the treatment of HIV-1 infected antiretroviral naïve subjects as determined by the achievement and maintenance of confirmed HIV-1 RNA <400 copies/ml through week 48. The secondary endpoint of the study is the achievement and maintenance of confirmed HIV-1 RNA <50 copies/ml through week 48.

The applicant submitted an interim report on a cohort of 184 patients who enrolled on or before October 20, 2003 and who received the study medication.

Virologic Failure for the interim analysis is defined as:

- Subjects who had maintained study drugs and had ≥ 400 copies/ml of plasma HIV-1 RNA at week 24 (never achieved <400 copies/ml)

- Subjects who had maintained study drugs and had >1000 copies/ml of plasma HIV-1 RNA at least on two consecutive visits after achieving <400 copies/ml of HIV-1 RNA on at least one occasion (rebound)

- Subjects who discontinued study drugs or the study and had ≥ 400 copies/ml of HIV-1 RNA on the last study visit prior to discontinuing study drug or the study

Plasma samples from virologic failure patients were phenotyped and genotyped at _____. Baseline genotyping was done on all virologic failure patients and baseline phenotyping was done on those virologic failure patients with evidence of genotypic resistance at baseline. Gilead submitted data on virologic failure patients is summarized in Table 1.

Table 1: Twenty-four week virologic failure isolates (n=14) from evaluated patients (n=184)

Isolate	TDF+FTC+EFV (N=93)	AZT+3TC+EFV (N=91)
Failures	8 (8.6%)	6 (6.6%)
Pt samples analyzed[1]	6	5
NNRTI resistance at BL[†]	2	1
No NNRTI resistance at BL	4	4
Any resistance developed	3/4	2/4
EFV-resist. developed	3/4	2/4
EFV-R* only	3/4	2/4
EFV-R+M184V	1/4	1/4
M184V developed	1/4	1/4
Wild type at VF	1/4	2/5

[1] Three patients undergoing virologic failure (VF) permanently discontinued prior to week 4. They had wild type virus at baseline. For lack of plasma samples, genotyping could not be done.

[†]BL = baseline

* EFV-R = efavirenz resistance

Data presented in Table 1 show that at week 24, fourteen patients met virologic failure criteria. Eight of the ninety three patients in the TDF/FTC arm and 6/91 in the combivir (AZT+3TC) arm underwent virologic failure. Out of these virologic failures, 3 patients (TDF/FTC, n=2; combivir, n=1) had no plasma sample for resistance analysis. In the remaining eleven virologic failure patients (TDF/FTC, n=6; combivir, n=5), resistance conferring mutations had been acquired. According to Gilead the most common form of resistance that developed was either an efavirenz resistance mutation (K103N) or

efavirenz resistance combined with resistance to 3TC or FTC (M184V). No thymidine analogue associated mutations or TDF associated mutation (K65R) developed in any of the virologic failures. Preliminary data from the interim analysis suggests that resistance development was similar between the two arms.

Conclusions: Microbiology studies presented in the original NDA# 21-356 for tenofovir and in the original NDA# 21-500 for emtricitabine clearly demonstrated the anti-HIV-1 activity of these drugs in a variety of T-cell lines and primary cells infected with laboratory and clinical isolates of HIV-1. Microbiology studies submitted to the current NDA # 21-752 for Truvada™ found the antiviral activity of the combination of TNV and FTC to be synergistic. However, these studies also show that the synergistic activity exerted by the two drug combination was short lived in that resistance to FTC emerges rapidly rendering it inactive and thus leaving TNV alone to exert antiviral activity in spite of the simultaneous presence of both of drugs on the infected cells in culture. Furthermore, the *in vivo* plasma concentrations of tenofovir are below the IC_{90} value, possibly limiting its effectiveness in the absence of this synergy. Over the course of time TNV conferring resistance mutations emerge with decreases in susceptibility not only to TNV itself but also extending additional resistance to FTC due to cross-resistance conferred by the TNV-associated K65R mutation. It is unknown how these events reflect *in vivo* where the therapeutic regimens include 3 drug combinations. A number of factors such as the potency of the third drug used in the combination, alterations in the rate and types of the development of resistance-conferring mutations, mutational interactions that may alter drug susceptibility/resistance, altered replication of mutant viruses and host immune pressure on the viral variants can individually and/or cumulatively mitigate the replication of HIV-1 *in vivo*.

Prior experience indicates that each of the two drugs, TNV and FTC, have a low genetic barrier in that a single point mutation in the HIV RT gene at codon positions 65 and 184 for TNV and FTC, respectively, makes the virus less/non susceptible to these drugs. Moreover, these mutations confer cross-resistance to all of the approved NRTIs of HIV-1, with the exception of zidovudine. Thus, the choice of these drugs for treatment also needs consideration from a resistance perspective to help preserve future options for therapy. It should be noted that in some clinical studies using certain drug combinations that included TNV with FTC or 3TC (an analogue of FTC) good clinical efficacy was observed, and, TNV/FTC or 3TC resistance conferring mutations emerged slowly in a small number of patients indicating the beneficial use of these drugs. However, in other clinical studies with triple NRTI combinations that included TNV as one of the components, a high percentage of patients developed the K65R mutation with loss of susceptibility and consequent increase in viral load. Thus, the emergence of resistance-conferring mutations and virologic failure depends on the combinations of antiretroviral

agents selected. The additional clinical trials that are in progress comparing the relative efficacy of TNV and FTC against active control arms will be the final arbiters of the choice of drug combinations.

Recommendations: The microbiology section of the draft package insert as revised and written by the FDA is acceptable. With respect to microbiology the drug is recommended for approval.

Applicant proposed Microbiology portion of the package insert

Microbiology

Mechanism of Action:

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of [illegible], is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro:

Tenofovir disoproxil fumarate Plus Emtricitabine: In combination studies evaluating the in vitro antiviral activity of tenofovir and emtricitabine together, synergistic antiviral effects were observed.

Tenofovir disoproxil fumarate: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease

inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5–2.2 μM).

Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} value for emtricitabine was in the range of 0.0013–0.64 μM (0.0003–0.158 μg/ml). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007–1.5 μM).

Drug Resistance:

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with VIREAD in combination with certain antiretroviral agents. In treatment-naïve patients treated with VIREAD + lamivudine + efavirenz, viral isolates from 7/29 (24%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, 14/304 (4.6%) of the VIREAD-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed

reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Tenofovir Disoproxil Fumarate: The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

FDA revised Microbiology portion of the package insert after review and evaluation of the application

MICROBIOLOGY

Mechanism of Action

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Antiviral Activity

Tenofovir disoproxil fumarate and emtricitabine: In combination studies evaluating the in vitro antiviral activity of tenofovir and emtricitabine together, synergistic antiviral effects were observed.

Tenofovir disoproxil fumarate: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5–2.2 μM).

Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (IC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007–1.5 μM).

Resistance

Tenofovir disoproxil fumarate and emtricitabine: HIV-1 isolates with reduced susceptibility to the combination of tenofovir and emtricitabine have been selected in vitro. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT gene.

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with VIREAD in combination with certain antiretroviral agents. In treatment-naïve patients 7/29 (24%) isolates from patients failing VIREAD + lamivudine + efavirenz at 48 weeks showed >1.4 fold (median 3.4) reduced susceptibility in vitro to tenofovir. In treatment-experienced patients, 14/304 (4.6%, Studies 902 and 907) isolates from patients failing VIREAD at 96 weeks showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 6/16 (37.5%) treatment-naïve patients with virologic failure showed >20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Cross-resistance

Tenofovir disoproxil fumarate and emtricitabine: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The K65R and/or M184V/I substitutions selected in vitro by the combination of tenofovir and emtricitabine are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

_____

Narayana Battula, Ph.D.
Microbiologist

Concurrence:

HFD 530/ Assoc Dir. _____ Date _____

HFD 530/TLMicro. _____ Date _____

Page Blank

Appears This Way
On Original

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

/s/

Narayana Battula
7/28/04 11:59:42 AM
MICROBIOLOGIST

NDA- micro review forTruvada original submission and supplements

Julian O Rear
7/28/04 01:05:07 PM
MICROBIOLOGIST

James Farrelly
8/2/04 09:33:44 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE CONFERENCE

Date of Meeting: June 4, 2004

NDA: 21-752

Drug: Tenofovir DF/Emtricitabine

Sponsor: Gilead Sciences, Inc.

Between: **Representatives of the FDA**
Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst
Jules O'Rear, Ph.D., Microbiology Team Leader
Jeff O'Neill, ACRN, Regulatory Health Project Manager

And: **Representatives of Gilead Sciences**
Martine Kraus, Director, Regulatory Affairs
Norbert Bischofberger, Research and Development
Andrew Cheng, Ph.D., M.D., Senior Director, Clinical Research
Michael Miller, Ph.D., Senior Director, Clinical Virology
Jay Toole, Ph.D., M.D., Senior VP, Clinical Research

Background: Teleconference held to discuss microbiology review comments sent to the Sponsor in a facsimile dated May 19, 2004.

Discussion:

Microbiology

(1) Does the Agency request resistance selection experiments for TFV, FTC and the combination of TFV and FTC in the backgrounds of wild-type, M184V and the K65R mutant HIV-1? Since K65R is already resistant to TFV and M184V is already resistant to FTC, we would propose not to study these specific combinations but instead provide RT genotypic analyses and viral growth data during selection at various drug concentrations for the other combinations.

(2) We wish to better understand the intent of the requested parallel resistance selections with AZT and 3TC and their objective in light of currently available literature information for these two compounds.

The sponsor described studies selecting in vitro virus resistant to the combination of tenofovir and emtricitabine. Virus harboring the M184I mutation rapidly emerged and was able to replicate in concentrations of tenofovir of 7 μM and 14 μM. Increasing the tenofovir concentrations to 28 μM and 56 μM suppressed replication. These concentrations are about ten fold higher than the IC_{50} values of failure isolates.

Dr. O'Rear stated that these results are consistent with genotypic analysis of failure isolates in some tenofovir/3TC-FTC containing regimens.

The Sponsor stated that these experiments are expected to be completed in the September/October 2004 timeframe.

The Division requested that the Sponsor provide an assessment as to what resistance patterns the Sponsor expects since there is uncertainty in regards to the resistance patterns that may be observed when tenofovir DF/emtricitabine are given together in combination with other drugs. The Division also requested that the Sponsor submit proposed wording for the Microbiology section of the Package Insert to reflect this information.

The Sponsor agreed to supply the assessment of resistance patterns and proposed wording for the Microbiology section of the Package Insert.

Clinical

The Division requested that the Sponsor submit proposed wording for the **Indications and Usage** section of the Package Insert to support the assertion that the efficacy and safety of emtricitabine is comparable to the efficacy and safety of lamivudine in order to "bridge" the applicability of the data generated in patients who were treated with tenofovir DF and lamivudine to the evaluation of the tenofovir DF/emtricitabine combination product.

The Sponsor agreed to supply the proposed wording for the **Indications and Usage** section of the Package Insert.

The Sponsor stated that they plan to submit a request for a Type B meeting to discuss a proposed Phase 3 development plan for tenofovir DF/emtricitabine combination product for the treatment of chronic hepatitis B and asked if submission of the request would interfere with the current review for NDA 21-752.

The Division stated that the request could be submitted at this time without impacting the review of NDA 21-752.

Action Items:

- The Sponsor will submit resistance selection experiments in wild type virus when the additional data is available, around September/October 2004.

- The Sponsor will submit an assessment as to what resistance patterns they expect to see when tenofovir DF/emtricitabine combination product is administered with other HIV drugs.

- The Sponsor will supply an assessment of resistance patterns and proposed wording for the **Microbiology** section of the Package Insert.

- The Sponsor will supply the proposed wording for the **Indications and Usage** section of the Package Insert in order to "bridge" the applicability of the data generated in patients who were treated with tenofovir DF and lamivudine to the evaluation of the tenofovir DF/emtricitabine combination product.

- The Sponsor will submit all available microbiology data from studies GS-99-903 and GS-01-934 in the FDA resistance template format by June 25, 2004.

- The Sponsor will provide a copy of an article on HIV-1 reverse transcriptase mutation selection during in vitro exposure to tenofovir alone or combined with abacavir or lamivudine and a copy of a poster on HIV DNA as a predictor of residual viremia as requested by Microbiology Team Leader.

- The Sponsor will provide a summary of principal 144-week safety data for study GS-99-903 and available safety data from [redacted] study GS-01-418.

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

/s/

Jeff ONeill
7/2/04 01:31:14 PM
CSO

Minutes from teleconference with Gilead to discuss Microbiology fax.

Russell Fleischer
7/2/04 01:55:07 PM
MEDICAL OFFICER