CENTER FOR DRUG EVALUATION AND RESEARCH

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 12, 2012
From	Kendall A. Marcus, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-752 S-30
Applicant	Gilead Sciences, Inc.
Date of Submission	December 14, 2011
PDUFA Goal Date	July 16, 2012
Proprietary Name / **Established (USAN) names**	TRUVADA® emtricitabine/tenofovir disoproxil fumarate
Dosage forms / Strength	Fixed dose tablet of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
Proposed Indication(s)	1. Pre-exposure prophylaxis of sexually acquired HIV-1 infection in adults at high risk
Recommended:	Approval

1. Introduction

In 1981, a description of the first case series of what we now know to be symptomatic infection with human immunodeficiency virus (HIV), or Acquired Immunodeficiency Syndrome (AIDS), manifesting as *Pneumocystis jiroveci* (*carinii*) pneumonia (PCP), was published in Morbidity and Mortality Weekly Report.[1] These cases represented the first recognition in the U.S. of a global epidemic of HIV infection that has grown over three decades to include approximately 34 million individuals worldwide at the end of 2010.[2] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 2.7 million (2.4 million–2.9 million) people were newly infected with HIV in 2010 alone.[3]

While the annual number of infections globally has declined slightly in recent years, the HIV epidemic in the United States has remained steady with little change in the annual incidence of new infections, about 50,000, since 2006.[4] About 75% of new U.S. infections occur in men, with minority populations bearing the heaviest burden of infection. Among women, African-Americans experience the highest HIV incidence rates. At the end of 2008, an estimated 1,178,350 persons were living with HIV in the U.S., including 236,400 (20.1%) whose infection was undiagnosed.

Unprotected anal sex between men who have sex with men (MSM) is associated with the greatest transmission risk in the United States. Although MSM represent just 2% of the overall U.S. population aged ≥ 13 years, they account for more than half (56-61%) of new HIV infections annually and represent nearly half of all persons living with HIV in this country.[5, 6] Moreover, while the overall HIV incidence in the U.S. has remained relatively stable in recent years, the estimated number of new infections among 13-29 year old MSM has increased

significantly (38%) from 2006 to 2009, largely driven by a 48% increase among young African-American MSM.[7]

HIV testing data collected as part of the National HIV Behavioral Surveillance (NHBS) system indicated an HIV prevalence of 19% among MSM in 2008.[8] Of the HIV-infected MSM, 44% were unaware of their HIV infection. HIV prevalence and lack of awareness of infection status were highest among young and minority MSM. More than half (55%) of MSM unaware of their infection reported not having an HIV test during the preceding 12 months. Among those who had tested negative during the preceding year, the study found a 6.9% prevalence of new infections.[9]

By comparison, HIV prevalence was reported as 3.3% amongst 933 minority females and their heterosexual partners (1021 partnerships) in a CDC-funded by the U.S. Centers for Disease Control and Prevention (CDC) and conducted during 2006-2007 in 16 cities within areas with high rates of poverty and HIV morbidity. [10] African-American and Hispanic women aged 18 to 50 years were recruited at venues and by peers for HIV testing in this study. Testing of all individuals confirmed HIV positive status in 21 individuals and identified 41 previously undiagnosed HIV infections. The majority of individuals diagnosed with HIV infection in this study were found to be in serodiscordant relationships.

The principal interventions used to date to prevent HIV transmissions have been voluntary HIV testing, risk reduction counseling, and promotion of condoms, but the effectiveness of these interventions has been variable. Studies show that persons aware of their HIV infection often take substantial steps to reduce their risk behaviors.[11] Particularly concerning, however, is a recent finding that almost half of the men who tested positive for HIV infection during an NHBS survey were unaware of their infection.[12] Persons who do not know they are infected are estimated to account for more than half of sexually transmitted HIV infections in the United States.[13]

Condoms are very effective in preventing sexually transmitted infections[14]; but consistent condom use is infrequent among MSM, thus limiting their utility in preventing HIV transmission. About half of the men surveyed in the NHBS reported unprotected anal intercourse in the past year, with approximately 12% engaging in unprotected anal sex with a partner of unknown HIV status. Barriers to condom use are varied, but may include personal preference, inability to negotiate condom use with a partner either due to partner pressure or intoxication from alcohol or drug use, or a disconnect between sexual behavior and risk perception. In a recent HIV testing program of MSM at a New England bathhouse, the majority (65%-75%) of men who engaged in unprotected sex did not believe their risk for HIV infection was high, despite the finding of a high prevalence of sexually transmitted infections.[15]

An alternative approach that has recently demonstrated efficacy in preventing HIV transmission on a population level is the treatment of HIV-infected individuals. The HPTN 052 trial of 3,400 heterosexual couples in Africa found that use of antiretroviral therapy in the HIV-infected partner reduced HIV transmission risk by 92%, in the context of intensive counseling and viral load monitoring.[16] Despite widespread efforts to diagnose HIV infections

in at-risk individuals and link them to healthcare, however, data from CDC suggest that only 51% of diagnosed persons stay in medical care; consequently, only an estimated 19% to 28% of all HIV-infected persons in the U.S. have a suppressed viral load. [17, 18]

Reasons for non-adherence with HIV care and antiretroviral therapy recommendations can vary. In a recent South African cross-sectional study, 20% of newly diagnosed HIV-infected individuals refused therapy; the leading reason for refusal was "feeling healthy" (37%), despite the presence of suppressed CD4+ cell counts and co-morbidities such as active tuberculosis.[19] In another study, about 40% of HIV-infected individuals in serodiscordant couples were not willing to initiate antiretroviral therapy for the purpose of preventing HIV transmission to their partners.[20] These HIV-infected individuals cited concerns about side effects, earlier development of resistance, social stigma, and pill burden as reasons.

In summary, despite the availability of several efficacious prevention modalities, the HIV epidemic in the U.S. continues unabated. Due to the limitations of any single modality as a means of achieving HIV eradication, a multipronged approach to HIV prevention is needed that should include the combination of condom promotion, risk reduction counseling, treatment of sexually transmitted infections (STIs), and increased uptake and retention of HIV-infected individuals in healthcare. However, given the limited effectiveness of these current prevention methods and the lack of an available vaccine, there remains an unmet medical need to identify and implement novel evidence-based approaches to HIV prevention that can augment the existing strategies. The use of approved antiretroviral drugs in high risk HIV-uninfected individuals as pre-exposure prophylaxis against HIV infection offers a potential intervention for primary HIV prevention that could potentially contribute to addressing this unmet need. For these reasons, efforts at development and evaluation of antiretroviral drugs for the indication of pre-exposure prophylaxis have been underway for over a decade.

2. Background

TRUVADA is a fixed-dose combination tablet of two antiretroviral drugs, emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF: tenofovir), and is currently approved, in combination with other antiretrovirals, for the treatment of HIV-1 infection in adults and pediatric subjects at least 12 years of age and older. TRUVADA was approved in 2004, while the individual components, emtricitabine (EMTRIVA) and tenofovir (VIREAD), were approved in 2003 and 2001, respectively. FTC and TDF are currently components of every preferred regimen recommended for HIV-1-infected treatment-naïve patients in the Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.[21]

With this application the Applicant proposes to indicate TRUVADA, once daily, in combination with safer sex practices, for the pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection in adults at high risk. In support of this indication, data from two large, prospective, randomized, double-blind placebo-controlled Phase 3 clinical trials, the iPrEx and Partners PrEP trials. Supportive safety data from a Phase 2 clinical trial of TDF for pre-exposure prophylaxis of sexually acquired HIV among initially uninfected MSM in the United States (CDC 4323) was also submitted.

The Partners PrEP trial was a, multicenter, international, randomized, double-blind, placebo-controlled trial of PrEP with once-daily oral TDF or FTC/TDF among HIV-uninfected individuals within an HIV-serodiscordant partnership, where the HIV-infected partner was not eligible for antiretroviral therapy per national guidelines. The trial was sponsored by the University of Washington with funding from the Bill and Melinda Gates Foundation. The trial enrolled 4,758 serodiscordant couples at 11 sites in Uganda and Kenya. The HIV-uninfected partners were randomized in a 1:1:1 ratio to receive TDF, FTC/TDF, or placebo. They were screened monthly for HIV infection and were provided with condoms, behavioral counseling and screening for other STIs at every trial visit.

The iPrEx trial was a multicenter, international, randomized, double-blind, placebo-controlled trial of once-daily oral FTC/TDF for HIV-1 prevention in MSM at high risk for acquiring HIV-1 infection. A total of 2499 subjects were randomized to receive either FTC/TDF (n=1251) or placebo (n=1248). The trial was sponsored by the Center for Disease Control (CDC) with funding from the Bill and Melinda Gates Foundation. Investigative sites were located in Brazil, Ecuador, Peru, Thailand, USA and South Africa. In addition to monthly HIV testing, trial subjects were provided with condoms, screening for other STIs, and active behavioral intervention, or counseling.

The effectiveness of antiretroviral drugs for HIV prevention was initially demonstrated by a series of controlled animal studies using macaque models of HIV transmission. These studies showed that treatment with oral or subcutaneous TDF, with or without FTC, either before or shortly after oral, rectal, vaginal, or intravenous inoculation with simian immunodeficiency virus (SIV) or SIV/HIV-1 chimeric virus (SHIV) prevented or delayed the onset of viremia. Collectively, nonclinical data showed that a single pre-exposure dose of FTC/TDF was not effective in preventing SIV or SHIV infection, demonstrating the need for post-exposure dosing, and that the combination regimen of FTC/TDF was more efficacious than single drug treatment and offered complete protection against an FTC-resistant virus containing M184V in macaques.[22, 23, 24] These observations, in addition to providing the initial evidence for efficacy of antiretroviral drugs when used for PrEP, also demonstrated the contribution of each of the two drugs, when used in combination as PrEP, in reducing the risk of HIV acquisition.

Other clinical data provides support that the combination of FTC and TDF are likely to be more effective in preventing sexual acquisition of HIV than either drug used alone: from a pharmacokinetic perspective, FTC reaches intracellular steady state concentrations in about 5 days of daily dosing, as compared to tenofovir, which reaches steady state only after 19 days of daily dosing. Important differences are also observed between the two drugs in terms of local tissue concentrations likely to be important in preventing HIV infection. FTC achieves higher concentrations in genital tissues relative to plasma than TDF (27-fold greater genital FTC compared to plasma vs. 2.5-fold greater genital TDF compared to plasma). However, TDF has a longer half-life in the genital tract than FTC (14 versus <2 days). Thus, concomitant use of FTC and TDF has been considered likely to provide advantages over use of either product alone; as a result, drug development for this indication has focused predominantly on this two-drug combination.

In addition to evaluating the efficacy of single versus combination drug strategies for HIV prevention, clinical trials have also sought to evaluate the efficacy of drugs in preventing HIV infection acquired through different modes of transmission. Trials evaluating the safety and efficacy of oral TDF, oral FTC/TDF and/or vaginal tenofovir gel have been or are being conducted in African women at risk of heterosexual HIV acquisition (CAPRISA 004, FEM-PrEP, Partners PrEP, CDC TDF2, VOICE), in African men at risk of heterosexual acquisition (Partners PrEP, CDC TDF2), in MSM globally (iPrEx), and in Thai injection drug users (Bangkok Tenofovir Study).

The status of completed and ongoing clinical trials of oral PrEP is summarized in Table 1 on the following page. Important considerations regarding the trials conducted but not submitted with this application include: the termination, by the DSMB of the VOICE clinical trial, of both the oral and microbicide gel formulations of TDF for lack of efficacy; halting of the FEM-PrEP trial that compared oral FTC/TDF to placebo for futility; the lack of power of the CDC TDF2 trial to convincingly demonstrate efficacy within gender subgroups; and the absence of trial data demonstrating activity of the FTC component of TRUVADA when added to TDF for PrEP. These issues will be addressed in the Risk/Benefit Assessment section of this memorandum.

Table 1: Completed and Ongoing Clinical Trials of Oral PrEP

TRIAL	SPONSOR	LOCATION	POPULATION	INTERVENTION	RESULTS
PHASE IIb, III					
iPrEx	NIH/DAIDS	USA, Brazil, Ecuador, Peru, S. Africa, Thailand	Adult MSM at high risk (N=2499)	Daily oral FTC/TDF	Risk reduction 42%
Partners PrEP	University of Washington	Kenya, Uganda	HIV serodiscordant couples (N=4747)	Daily oral TDF or FTC/TDF	Risk reduction TDF 67% FTC/TDF 75%
CDC TDF2	CDC	Botswana	Adult heterosexual men and women 18-39 (N=1219)	Daily oral FTC/TDF	Risk reduction 62%
FEM-PrEP	FHI	Kenya, South Africa, Tanzania	Adult women at high risk 18-35 (N=2120)	Daily oral FTC/TDF	Stopped for futility 04/11
VOICE (MTN 003)	NIH/DAIDS	Uganda, South Africa, Zimbabwe	Adult women 18-45 (N=5029)	Daily oral FTC/TDF or TDF or tenofovir vaginal gel	- Oral TDF and tenofovir gel arms stopped 09/11 - Oral FTC/TDF and oral placebo arms ongoing
Bangkok TDF Study (CDC4370)	CDC	Thailand	Adult injection drug users (N=2400)	Daily TDF	Ongoing
ANRS IPERGAY	ANRS	Canada, France	Adult MSM (N=300 initial; 1900 total)	FTC/TDF dosed at time of intercourse	Ongoing
PHASE II					
CDC 4323	CDC	USA	Adult MSM 18-60 (N=373)	Daily TDF (immediate vs. delayed treatment)	7 HIV seroconversions, none on trt
FHI PrEP	FHI	Ghana, Cameroon, Nigeria	Adult women at high risk 18-35 (N=936)	Daily oral TDF	8 HIV seroconversions (TDF 2, placebo 6)
HPTN 069	NIH/DAIDS	USA	Adult MSM (N=400)	Daily MVC or MVC/FTC or MVC/TDF or FTC/TDF	Enrolling
HPTN 067	NIH/DAIDS	South Africa, Thailand	Adult men and women (N=360)	Intermittent dosing of FTC/TDF	Enrolling
PHASE I					
SSAT 040	St. Stephen's AIDS Trust	UK	Adult men and women (N=66)	Single dose intramuscular TMC278LA	Enrolling

Abbreviations: ANRS=French National Agency for Research on AIDS and Viral Hepatitis; CDC=U.S. Centers for Disease Control; DAIDS=Division of AIDS; FHI=Family Health International; MTN=Microbicides Trials Network; MVC=maraviroc; NIH=U.S. National Institutes of Health

3. CMC/Device

No changes to the chemistry, manufacturing, and controls for the TRUVADA tablet are proposed with this application. The currently manufactured and approved TRUVADA tablet for the treatment of HIV infection will also be utilized for the PrEP indication.

4. Nonclinical Pharmacology/Toxicology

No new toxicological studies were submitted with this application. The toxicological profiles of FTC and FTC/TDF are well-characterized in multiple animal species and the findings are applicable for consideration of the use of these agents in combination. Data from controlled clinical studies and extensive post-marketing experience of combination regimens of FTC and TDF demonstrates acceptable tolerability and safety profiles to support use in the adult population. (*For additional details, please refer to the Pharmacology/Toxicology review completed by Pritam Verma, PhD.)*

5. Clinical Pharmacology/Biopharmaceutics

Each TRUVADA tablet contains 200 mg of FTC and 300 mg of TDF. FTC is a synthetic nucleoside analog of cytosine, while TDF is an analog of adenosine 5'-monophosphate. FTC and TDF belong to the class of HIV drugs known as nucleos(t)ide reverse transcriptase inhibitors (NRTI). The drugs undergo intracellular phosphorylation to their active forms, FTC-5'-triphosphate (FTC-TP) and TFV-5'- diphosphate (TFV-DP), respectively. A single dose of FTC/TDF delivers intracellular TFV-DP and FTC-TP concentrations that are approximately 15% and 35% of the expected steady-state intracellular concentrations, respectively. As previously described, FTC reaches intracellular steady state concentrations in about 5 days, as compared to 19 days for TDF. Of note, the intracellular half-life of TFV-DP is much longer than the plasma half-life of TDF (87-150 hours versus 18.7 hours, respectively). Likewise, the intracellular half-life of FTC-TP is longer than the plasma half-life of FTC (39-50 hours versus 8 hours, respectively). FTC achieves higher concentrations in genital tissues relative to plasma than TDF (27-fold greater genital FTC compared to plasma vs. 2.5-fold greater genital TDF compared to plasma). However, TDF has a longer half-life in the genital tract than FTC (14 versus <2 days).

The primary route of elimination of both drugs is renal excretion, through a combination of glomerular filtration and active tubular secretion. Because of their route of excretion, the need for dosage adjustment of both drugs for renal impairment, and the increased risk of further decline in renal function in renally-impaired individuals who use FTC/TDF, use of TRUVADA for a PrEP indication is not recommended for individuals with creatinine clearance below 60 ml/min. A decline in renal function following initiation of FTC/TDF for PrEP should prompt evaluation for the cause and reassessment of the potential risks and benefits of ongoing use of FTC/TDF to the individual. The pharmacokinetics of TDF are not altered by hepatic impairment and have not been studied for FTC. No pharmacokinetic differences due to race or gender have been identified for either drug.

Drug-drug interaction studies were previously conducted with TDF. The studies have primarily been conducted with other antiretroviral agents, but interactions with oral contraceptives, methadone, and tacrolimus have also been evaluated. Importantly, no

interaction was observed with oral contraceptives, methadone or tacrolimus. The potential for drug interactions with FTC has been studied in combination with zidovudine, indinavir, stavudine, famciclovir, and TDF. No clinically significant drug interactions were noted for concomitant administration of FTC with any of these drugs.

Regarding potential drug interactions with other renally-excreted drugs, Section 7.4 of the product label currently states, "Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion [See Clinical Pharmacology (12.3)]. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir."

Exploratory analyses in the iPrEx trial evaluated renal function and changes in bone mineral density in subjects receiving both FTC/TDF and either acyclovir or valacyclovir. No apparent relationship between coadministration of these drugs and declines in renal function or bone mineral density were observed.

6. Clinical Microbiology

Please see the Clinical Virology review by Damon Deming, Ph.D., for a complete review of resistance data.

The emergence of drug-resistant HIV-1 variants in association with oral PrEP is both an individual and a public health concern. Individuals who acquire HIV while taking PrEP who have viral strains with drug resistance will have fewer treatment options. If these same individuals then transmit resistant strains to susceptible individuals, drug resistance could theoretically become widespread. However, in the iPrEx and Partners PrEP trials, as well as in other clinical trials of oral PrEP conducted to date, resistance-associated substitutions conferring drug resistance in HIV-1 viral variants have developed only among subjects who were enrolled in the trials with undiagnosed acute HIV-1 infection at baseline (i.e., negative rapid HIV antibody test at enrollment).

In the iPrEx trial, resistance-associated substitutions conferring resistance to FTC were detected after 4 weeks of FTC/TDF prophylaxis in 2/2 subjects who were acutely infected at the time of enrollment; however, it is only clear that resistance developed following FTC/TDF exposure in one of these subjects. In the Partner's PrEP trial, 14 subjects (TDF 5, FTC/TDF 3, placebo 6) were enrolled with undiagnosed acute HIV-1 infection. Three of the eight subjects randomized to the TDF or FTC/TDF arms had resistance-associated substitutions detected when HIV was diagnosed during the trial; only 2/3 clearly developed resistance-associated substitutions during the trial. No resistance was detected among the 5 remaining subjects in the TDF and FTC/TDF groups who were HIV-infected at baseline; however, PK data with which to assess adherence in these subjects was lacking.

In both pivotal trials, among the 75 subjects randomized to active treatment who seroconverted post-enrollment and for whom evaluable RNA data are available (48 in the FTC/TDF group of iPrEx and 15 and 12 in the TDF and FTC/TDF groups of Partners PrEP, respectively), no evidence of substitutions conferring NRTI resistance was observed.

7. Clinical/Statistical- Efficacy

Please see the statistical review by Tom Hammerstrom for a complete review of efficacy.

The efficacy of FTC/TDF for pre-exposure prophylaxis of sexually-acquired HIV-1 in adults at high risk is supported by two large clinical trials, the iPrEx and Partners PrEP trials, previously summarized in this memo. FDA review of data from these trials supports that each trial robustly demonstrated the superiority of FTC/TDF over placebo in preventing HIV-1 acquisition through sexual exposure, when offered as part of a comprehensive prevention strategy. Important elements of these trials included their prospective, randomized, double-blind designs, with provision of identical prevention strategies to all treatment arms. These strategies included monthly HIV testing, risk reduction counseling, provision of condoms, and screening for and treatment of STIs. Many sensitivity analyses were performed on the data, including analyses that examined the impact on risk reduction of: post-exposure prophylaxis (PEP) initiation; treatment of HIV-1 infected index partners; and high risk behaviors reported by subjects in each treatment arm. These sensitivity analyses all supported the conclusion that FTC/TDF significantly reduces the risk of sexual acquisition of HIV-1 in adults at high risk.

In these populations and trial settings, FTC/TDF reduced the risk of HIV-1 infection in the iPrEx trial by 42% (95% CI 18-60%) relative to placebo in the modified intent-to-treat analysis, and by 75% (95% CI 54-86%) relative to placebo in the Partners PrEP trial. Risk reduction was observed across most subpopulations regardless of gender, race, age, region, or baseline risk characteristics; importantly, statistically significant risk reductions were observed for both males and females in Partners PrEP. Most notably, FTC/TDF was demonstrated to be effective in those MSM who reported engaging in unprotected anal intercourse, thus highlighting the efficacy of FTC/TDF for PrEP in adults at particularly high risk of HIV acquisition.

Use of PrEP by high risk individuals has led to concerns that PrEP will be perceived by some users to be a replacement for highly effective safer sex practices, such as condom use, and lead to an increase in high risk sexual behaviors. It is postulated that this will in turn, increase rather than decrease individuals risk for acquiring HIV. In the iPrEx and Partners PrEP trials, risk compensation, as evidenced by self-reported risk behavior and by the incidence of STIs, did not appear to occur. In fact, the incidence of STIs either remained stable or declined over the course of each trial.

The relationship between drug concentration and the protective effect of FTC/TDF against HIV infection was explored by both the iPrEx and Partners PrEP trial investigators in post-hoc subgroup case control studies nested within the clinical trials. The FDA Clinical Pharmacology and Pharmacometrics review teams performed an independent analysis of the PK data obtained from these trials to examine the relationship of drug exposure (adherence) to risk reduction;

the results are summarized here. *See Clinical Pharmacology review by Ruben Ayala, Pharm.D and Jiang Liu, Ph.D., for a detailed description of these and other efficacy analyses*.

For the iPrEx trial, submitted PK data contained plasma and intracellular concentrations of FTC and TDF closest to the date of seroconversion for 48 HIV seroconverters in the FTC/TDF group. PK data was also obtained from 144 matched uninfected controls from the FTC/TDF arm. Only 8% of HIV seroconverters had measurable levels of intracellular TFV-DP at the visit closest to the time of seroconversion as compared to 38% of the matched uninfected controls ($P< 0.0001$; 11 replicated subjects were excluded). Given the 21-day half-life of intracellular TFV-DP in peripheral blood mononuclear cells (PBMCs), non-measurable intracellular concentrations are indicative of poor adherence to trial drug.

In order to assess the impact of drug exposure on efficacy, the distribution of subjects with detectable TFV-DP concentrations among the 133 uninfected subjects (38% measurable) was extrapolated to all uninfected subjects within the FTC/TDF arm of the iPrEx trial (N=1176). Based on this extrapolation, HIV seroconversion rates and risk reductions were calculated for the entire trial population. In summary, the relative risk reduction for FTC/TDF in subjects with measurable TFV-DP, as compared to placebo, was 87.5%. In contrast, subjects with non-measurable TFV-DP demonstrated limited additional protection from HIV acquisition (14.5%) compared with placebo. FDA then calculated seroconversion rates for subjects with low intracellular TFV-DP concentrations (<11 fmol/M cell) and high measurable concentrations (≥11 fmol/M cell). In this analysis, the relative risk reduction was estimated to be 76.1% for the low measurable group (<11 fmol/M cell) and 94.9% for the high measurable group, suggesting that adherence, as measured by intracellular drug levels, is directly correlated with risk reduction. Similar analyses conducted with plasma TDF levels in the Partners PrEP trial resulted in consistent findings.

Analyses of the iPrEx trial data also explored the relationship of demographics and baseline characteristics with detectable drug levels as measures of adherence and with seroconversions. Age over 25 years, educational attainment beyond high school and self-report of high risk anal sex were the covariates that most strongly correlated with adherence and efficacy.

8. Safety

Please see the clinical review by Peter Miele, M.D. for a complete review of safety.

The safety of TRUVADA for a PrEP indication is supported by the review of safety data from the iPrEx and Partners PrEP trials. Additional supportive safety data was provided by the Phase 2 CDC 4323 trial conducted in the United States which enrolled about 400 MSM.

In these trials, FTC/TDF was generally well tolerated and no new safety issues were identified. No significant difference was noted in the incidence of treatment-emergent adverse events by gender. Adverse event rates were slightly higher for subjects ≥40 years across both pivotal trials compared with subjects younger than 40, but the rates within each age group were comparable between treatment arms. Trial events pertinent to the safety evaluation, including deaths, serious adverse events, adverse events leading to drug discontinuation and adverse events of moderate to severe toxicity were balanced between the active and placebo groups in

each trial. In the iPrEx trial, unintended weight loss, nausea, and abdominal pain were reported slightly more often in subjects receiving FTC/TDF. Permanent drug discontinuations due to adverse events were infrequent in the both trials (4% in iPrEx and <1% in Partners PrEP) and were generally balanced between treatment groups. In both arms of the iPrEx trial, study drug was most commonly stopped or interrupted for psychiatric disorders, the vast majority of which were not considered to be treatment-related. Of note, no imbalance between treatment arms in psychiatric adverse events, including depression, was observed. Increased creatinine or decreased creatinine clearance resulted in treatment interruptions or discontinuation infrequently; in all but one subject, changes resolved promptly and subjects often resumed study medication without recurrence. No cases of acute renal failure or Fanconi syndrome were reported. No evidence of hepatic flares was noted among the 19 study subjects with chronic or acute hepatitis B infection followed in the two trials.

No significant differences or trends in clinical laboratory parameters were noted among the treatment groups in both pivotal trials. Among subjects randomized to FTC/TDF in both trials, hypophosphatemia was the most common ≥ Grade 2 treatment-related adverse event (causality as determined by the site investigators), reported in 4% of subjects in the iPrEx trial and 14% of subjects in the Partners PrEP trial (compared with 3% and 13% in the placebo groups, respectively). For both trials, the rates of graded serum creatinine or serum phosphorus laboratory abnormalities were comparable among the treatment groups, as were the rates of proteinuria and glycosuria on urine dipstick. Mean changes from baseline in serum creatinine, creatinine clearance, or serum phosphorus were small or negligible at all time points for all treatment groups in both trials. In the Partners PrEP trial, moderate to severe neutropenia was observed slightly more frequently in subjects receiving FTC/TDF compared with placebo, although the differences were small.

Changes in bone mineral density were evaluated in DEXA scan sub-studies in both the iPrEx and CDC 4323 trials. In these sub-studies, small but significant decreases in bone mineral density (BMD) compared to baseline were noted in the TDF-based arms relative to placebo. Of note, similar findings were reported for the CDC TDF2 trial in heterosexual men and women treated with FTC/TDF. Among the 45 subjects in the iPrEx trial with ≥5% BMD decrease from baseline at the spine, five (all in the FTC/TDF group) also had evidence of treatment-emergent graded hypophosphatemia. DEXA scans obtained six months after discontinuation of treatment in the iPrEx trial, however, suggested that the BMD decreases observed with FTC/TDF use were reversing towards baseline levels. Importantly, no differences in fracture rates were observed between treatment groups across multiple trials. The vast majority of fractures reported in the three submitted trials were trauma-related, with wide variation in time to onset.

In the Partners PrEP trial, all women who became pregnant were instructed to stop study drug as soon as they had a positive pregnancy test. Of note, 5 of the 45 seroconversions in women occurred during treatment interruptions for pregnancy. No significant between-group trends were noted in pregnancy outcomes among the 267 women who became pregnant during treatment, although the relative pregnancy rate was lowest and the spontaneous abortion rate highest in the FTC/TDF arm. In contrast, the spontaneous abortion rate was lowest in the TDF arm as compared to both the placebo and FTC/TDF arms. These observations must be

interpreted in the context that women were tested for pregnancy on a monthly basis, which likely resulted in frequent detection of chemical pregnancies. Additionally, no analyses were conducted with respect to age, concomitant medication use or other factors that may explain any potential differences.

9. Advisory Committee Meeting

An Antivirals Drugs Advisory Committee (AVDAC) meeting was convened on May 10, 2012. The majority of the committee agreed that the current application supports a favorable risk-benefit assessment adequate to approve TRUVADA for a PrEP indication in HIV-uninfected MSM (vote 19-Yes, 3-No) and in HIV-uninfected partners in serodiscordant couples (vote 19-Yes, 2-No, 1-Abstain). Those who voted "Yes" stated that there was positive efficacy data demonstrated in both populations. Those who voted "No" noted concerns about placing individuals at undue risk and also expressed that there was not sufficient efficacy data because of insufficient data in African-American MSM subjects and no African-American female representation in the trials. The majority of committee members also agreed that the current application supports a favorable risk-benefit assessment adequate to approve TRUVADA for a PrEP indication in other individuals at risk for acquiring HIV through sexual activity.

Additionally, there was a general agreement that further efficacy and safety data are needed through post-marketing observational studies to address long-term use of TRUVADA in terms of kidney toxicity and drug resistance.

Committee members emphasized that baseline HIV testing prior to prescribing TRUVADA for a PrEP indication is crucial and that initiation of TRUVADA in an individual with undiagnosed HIV-1 infection is an important safety issue. Some committee members favored implementation of a Risk Evaluation and Mitigation Strategy that would require physicians to document a negative HIV test result as a condition of safe use. Other committee members felt this would create unnecessary barriers to access of the drug to individuals most in need. One committee member thought addition of language about the importance of confirming a negative HIV test prior to initiation of TRUVADA for a PrEP indication to the current Boxed Warning could address this safety concern.

FDA noted that a requirement to document a negative HIV test as a condition of use would essentially result in restricted distribution, negatively impacting the availability of the TRUVADA for both treatment and prevention. FDA provided reasons that restricted distribution would not be feasible or appropriate for this indication given the current availability of the drug for treatment. The committee thus recommended that the Applicant take a more active approach to educating prescribers and consumers. Notable recommendations to address education included creation of a checklist and/or contract between provider and consumer detailing the expectations of each and education of non-HIV health care providers on how to recognize the symptoms of acute HIV seroconversion.

10. Pediatrics

The Applicant submitted a pediatric plan as part of this supplement. A waiver was requested for children <16 years of age because necessary studies are impossible or highly impracticable

and because the product is unlikely to be used in a substantial number of the pediatric age group for which a waiver is being requested (Federal Food, Drug and Cosmetic Act (FDCA), as amended by PREA, Sections 505B(a)(4)(B)(i) and Section 505B(a)(4)(B)(iii), respectively). A partial waiver was requested for adolescent females 16 to <18 years of age and a deferral of pediatric studies was requested for adolescent males 16 to <18 years of age.

The Pediatric Review Committee (PeRC) reviewed this application on April 18, 2012 and concurred with the full waiver in pediatric subjects from birth to16 years because the trials would be impossible or highly impractical. It was noted that according to 21 CFR 201.57(f)(9)(i), the pediatric age group is defined as "birth to 16 years"; therefore, trials conducted in adolescents ≥16 years are not required under the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

Section 505-1 of the FDCA gives the Secretary the authority, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug, to determine that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of a drug outweigh the risks of the drug. A REMS is being required for TRUVADA for a PrEP indication because of the risk for development of drug-resistant HIV-1 variants if TRUVADA for PrEP is initiated or continued in individuals with unrecognized HIV-1 infection. Development of drug-resistant HIV-1 variants may limit treatment options for an individual who seroconverts while taking TRUVADA for a PrEP indication and increase their risk of transmitting drug-resistant HIV-1 variants to others. If this were to occur, the individual taking TRUVADA would not receive any potential benefit, because HIV-1 infection has already occurred. Additionally, they would be exposed to the potentially serious risk of development of drug-resistant HIV-1 variants. Because the drug product is already approved and widely used for the treatment of HIV-1 infection, a restrictive REMS that links distribution of the drug to documentation of a negative HIV test result is not feasible.

A comprehensive management strategy is necessary in order to reduce the occurrence of an individual with unrecognized HIV-1 infection initiating or continuing to take TRUVADA for a PrEP indication. This strategy includes education of the individual in order to minimize their risk of acquiring HIV as well as regular monitoring by the prescriber of the individuals HIV status with appropriate diagnostic HIV testing. Therefore, the goals of the REMS are to inform and educate prescribers, other healthcare professionals, and uninfected individuals at high risk for acquiring HIV infection through sexual activity about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take TRUVADA for a PrEP indication if seroconversion has occurred, in order to reduce the risk of development of resistant HIV-1 variants
- The fact that TRUVADA for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and other preventive measures should also be used

The elements of the REMS will include:

• A TRUVADA Medication Guide, which will be dispensed with each TRUVADA prescription in accordance with 21 CFR 208.24
• Element to Assure Safe Use (ETASU), consisting of:
    - Training and education materials made available to prescribers who prescribe TRUVADA for a PrEP indication. This will be done via an online website or by print training modules available as hard copy, upon request
    - Targeting training efforts to prescribers most likely to prescribe PrEP (primary care physicians, internists, family practitioners, infectious diseases specialists, obstetrician-gynecologists, and addiction specialists)
    - Dissemination of a Safety Information Fact Sheet about the potential and known safety risks with TRUVADA for a PrEP indication to select professional organizations to disseminate to healthcare providers bi-annually for 3 years
    - Provision of the Safety Information Fact Sheet to MedWatch at the same time it is provided to the select professional organizations
    - Quarterly publication of journal information pieces
    - Distribution of a Dear Healthcare Provider (DHCP) letter within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 6, 12 and 24 months
    - Provision of an education slide deck for face-to-face meetings between pharmaceutical representatives and prescribers
    - Provision of a voluntary Healthcare Prescriber-Individual Agreement Form for initiating TRUVADA for PrEP to be signed by both parties and placed in an individual's medical record
        - Although use of this element will not be made mandatory, it may nonetheless serve as a tool for the prescriber and uninfected individual to facilitate discussion and promote understanding about the important safety risks associated with TRUVADA for a PrEP indication.
    - Provision of a voluntary Checklist for Prescribers as a reminder about the management of an individual considering or taking TRUVADA for a PrEP indication, including recommended screening and baseline tests, signs and symptoms of acute HIV infection, HBV vaccination as needed, and testing for sexually transmitted infections. The Checklist can also be placed in an individual's medical record to indicate that the prescriber has taken the necessary steps to ensure TRUVADA for a PrEP indication will be used appropriately.
    - The materials listed in the ETASU will be available through the TRUVADA REMS program website and will remain on the website for a period of 3 years following product approval.

During development of the REMS for TRUVADA for a PrEP indication, elements of the REMS, including those that would restrict distribution of TRUVADA for a PrEP indication unless certain conditions of safe use had been met, were extensively discussed in the following internal and external settings:

- FDA Regulatory Briefing June 10, 2011
- Center Director Briefing July 14, 2011
- Forum for Collaborative HIV Research open public meeting August 19, 2011

- REMS Oversight Committee (ROC) meeting March 2, 2012
- Antiviral Drugs Advisory Committee meeting May 10, 2012
- Center Director Briefing May 16, 2012

In totality, the consensus opinion derived through feedback from multiple levels of FDA leadership and from diverse stakeholders, including primary care and HIV/STI healthcare providers, patient advocates, researchers, industry representatives, behavioral scientists and others is that a restrictive REMS should not be required. A restrictive REMS would be highly impractical and virtually impossible to enforce. Additionally, it would create unnecessary barriers to healthcare to those most in need of interventions, as well as potentially prevent HIV-infected patients access to life-saving treatments. Some of the specific restrictive elements proposed and discussed included:

- Separate branding and packaging of TRUVADA for a PrEP indication with the goal of creating two separate access pathways for TRUVADA, one for treatment of HIV-infected patients without restrictions and one for PrEP for uninfected individuals that would have restricted access unless certain conditions of safe use are documented. In reality, this system could easily be circumnavigated through provision of a prescription for TRUVADA for treatment to an individual initiating PrEP. Successful enforcement of such a system would require pharmacies dispensing TRUVADA to have the authority to refuse to dispense TRUVADA if they could not verify that a prescription for TRUVADA for treatment was being dispensed to an HIV-infected patient. This is not only unworkable due to the wide variety of pharmacies dispensing TRUVADA, including mail order and on-line pharmacies, and the different manual or electronic-based mechanisms available to healthcare providers to prescribe drugs, but also due to privacy issues surrounding such an inquiry and other legal issues regarding the ability to grant pharmacists such authority. Finally, TRUVADA is also used for post-exposure prophylaxis (PEP), for both occupational and non-occupational exposure. Because PEP must be taken within 72 hours of potential HIV exposure, access cannot be restricted; therefore, such a system would also have to make provision for this other group of uninfected individuals to have unrestricted access to TRUVADA.
- Mandatory prescriber education/certification – In contrast to required certification for prescribing medications such as REVLIMID (lenalidomide), which has a narrowly-defined indication and is prescribed by a relatively small group of specialized physicians, this approach is highly impractical or unworkable due to the wide variety and number of healthcare providers who may wish to or need to prescribe TRUVADA for a PrEP indication; in the United States, there are over 200,000 primary care physicians alone.[25] Additionally, some prescribers may need to prescribe TRUVADA for a PrEP indication to only one or two individuals and such mandatory education would serve as a barrier. Again, this system could be easily circumnavigated under any circumstance, unless access to TRUVADA for treatment was also restricted.
- Mandatory documentation of HIV negative status prior to initiation of TRUVADA for a PrEP indication and for receipt of initial or refill prescriptions. It was proposed that the Applicant could be made responsible for monitoring compliance with this requirement rather than have pharmacies verify HIV negative status prior to dispensing medication. This is unworkable for the same reasons described above, again due to the number of

physicians who may prescribe TRUVADA for a PrEP indication, due to the inability to enforce without pharmacy involvement, and the added burden to distinguish between clinicians who are prescribing TRUVADA for HIV-1 treatment and for a PrEP indication, unless access to both is restricted.

12. Labeling

Please see the clinical review by Peter Miele, M.D. for a complete summary of the revisions to the U.S. product information.

Revisions to the labeling of TRUVADA to add a PrEP indication included the following important elements:

- Addition to the Boxed Warning of statements that TRUVADA for a PrEP indication must only be used in individuals confirmed to be HIV-negative immediately prior to initial use and periodically during use and that TRUVADA should not be initiated for a PrEP indication if signs or symptoms of acute HIV infection are present until negative infection status is confirmed.
- That TRUVADA is indicated, in combination with safer sex practices, for pre-exposure prophylaxis of sexually acquired HIV-1 infection in individuals at high risk
- A list of factors to consider when evaluating the risk of individuals for acquiring HIV-1 through sexual contact.
- The important elements of healthcare provider management of individuals prescribed TRUVADA for a PrEP indication, including education of the individual about the importance of medication adherence and safer sex practices, recommended HIV-1 testing methods and intervals, timing of initiation of PrEP and other recommendations for management of the individual taking PrEP.
- Addition of efficacy and safety data from the clinical trials used to support the PrEP indication.
- Revision of the pregnancy section to provide recommendations about use of PrEP if pregnancy should occur and addition of pregnancy outcome data from the Antiretroviral Pregnancy Registry.
- Creation of a Medication Guide to inform HIV-infected patients and uninfected individuals taking TRUVADA for a PrEP indication about the risks associated with the use of TRUVADA and directions for use for individuals taking TRUVADA for a PrEP indication.

13. Recommendations/Risk Benefit Assessment

The efficacy of FTC/TDF in the prevention of sexual acquisition of HIV-1 infection in uninfected individuals at risk is supported by the two large clinical trials, iPrEx and Partners PrEP, submitted with this application. In both trials, PrEP was utilized as an adjunctive intervention to monthly HIV testing, screening for and treatment of other STIs, behavioral counseling and provision of condoms at each study visit. Other large clinical trials have inconsistently demonstrated efficacy; however, drug level analyses conducted in those trials as well as in iPrEx and Partners PrEP all support that efficacy of PrEP is strongly correlated with

adherence. Notably, the majority of women in the failed FEM-PrEP trial did not perceive themselves to be at risk for acquisition of HIV; this disconnect between behavior and perceived risk may have resulted in the poor adherence observed in FEM-PrEP through drug level analyses. Also of note are the results of an adherence monitoring and counseling sub-study of Partners PrEP.[26] In this sub-study, subjects received the additional measures of unannounced home-based pill counts, placement of Medication Event Monitoring System (MEMS) caps on medication bottles to monitor compliance, couples-based adherence counseling and additional cognitive-behavioral counseling if adherence was found to be less than 80%. Remarkably, no subjects receiving FTC/TDF or TDF seroconverted as compared to 14 placebo subjects in this sub-study. These finding highlight the importance and impact of engagement in healthcare and ongoing adherence and risk counseling as part of a comprehensive strategy of HIV prevention.

While the two Phase 3 clinical trials submitted in support of the proposed indication were conducted in target populations at particularly high risk for acquiring HIV, the results demonstrate the effectiveness of FTC/TDF preventing HIV transmission through the primary sexual exposure routes (rectal sex in iPrEx and penile/vaginal sex in Partners PrEP) relevant to all sexually active persons, regardless of relationship status. As a result, the PrEP indication for TRUVADA will not be limited to those populations defined by the pivotal trials, but instead will be extended to all sexually active adults considered to be at high risk for infection. High risk for these individuals may be determined by a variety of factors, such as local HIV prevalence rates, involvement in high-risk sexual networks, or other established epidemiological risk factors.[27, 28, 29]

Resistance-associated substitutions were observed only in individuals enrolled in iPrEx and Partners PrEP with unrecognized HIV infection. Analysis of HIV-1 isolates from individuals who became infected while taking FTC/TDF or TDF in iPrEx and Partners PrEP failed to identify resistance-associated substitutions that developed following seroconversion, consistent with the finding that study subjects who seroconverted were clearly not adherent to medication. Selection of resistance among trial participants may have been minimized due to monthly monitoring for seroconversion.

The impact of PrEP on resistance development outside of a clinical trial setting is difficult to predict, but development of resistant HIV-1 viral variants is expected among infected individuals using PrEP. To minimize and monitor this important safety issue, several measures are being taken. A Risk Evaluation and Mitigation Strategy for TRUVADA for a PrEP indication has been developed, central to which is the provision of training and educational materials for healthcare providers who prescribe PrEP. Revisions have been made to the U.S. package insert to include a Boxed Warning about confirming HIV negative status prior to initiation of PrEP, as well as a description of the important elements of healthcare provider management of individuals using PrEP and factors to consider when evaluating an individual for PrEP use. A Medication Guide has been created for TRUVADA to describe the safety risks associated with TRUVADA and to provide directions about the proper use of TRUVADA for a PrEP indication. In addition to these measures, the Applicant will be required, through a postmarketing requirement, to evaluate viral isolates from participants in PrEP demonstration

projects who seroconvert while taking FTC/TDF for evidence of resistance-associated substitutions.

Two other post-marketing requirements will be issued with approval of the PrEP indication. Because limited data are available regarding the use of TRUVADA during pregnancy, and it is anticipated that the product will be used by pregnant women for PrEP, the Applicant will be required to collect data on pregnancy outcomes in women who become pregnant while taking TRUVADA for a PrEP indication. Additionally, while potential renal and skeletal adverse events are well described for TRUVADA when used to treat HIV-1-infected patients, TRUVADA for a PrEP indication will be used in a new population. Accordingly, the Applicant will be required to evaluate levels of adherence and correlate them to renal and skeletal events, and to resistance development.

The Applicant has also agreed to validate an adherence questionnaire in order that a more reliable tool than self-reporting could potentially be made available to predict compliance. Finally, the Applicant has agreed to collect and summarize nationally representative drug utilization data, such that use of TRUVADA for a PrEP indication and the individuals using TRUVADA for a PrEP indication can both be characterized.

Overall, FTC/TDF appeared to be well tolerated amongst HIV-uninfected individuals and no new safety issues were identified in the review of this application. In general, adverse events appeared to be balanced between active and control arms. In iPrEx, nausea, abdominal pain and unintended weight loss were reported slightly more often in subjects receiving FTC/TDF. Discontinuations were infrequent and generally balanced between groups. Increases in creatinine or decreases in glomerular filtration rate were observed in less than 1% of subjects, and promptly returned to baseline following treatment interruption or discontinuation in all but one subject. No cases of acute renal failure or Fanconi syndrome were identified. Similar to findings in HIV-infected patients, small but statistically significant mean decreases in BMD relative to placebo were observed in the iPrEx and CDC 4323 trials. DEXA scans obtained six months after discontinuation of treatment in the iPrEx trial showed that the BMD decreases observed in the FTC/TDF arm were reversing towards baseline levels. Importantly, in both iPrEx and Partners PrEP, bone fractures were trauma-related and balanced between treatment arms.

Approval of TRUVADA for use as pre-exposure prophylaxis of sexually-acquired HIV infection in adults at high risk will provide healthcare providers and high risk individuals with another prevention modality to help reduce, both on an individual and a population level, ongoing HIV transmission in the United States. Engagement of an individual in a comprehensive prevention program that includes PrEP should lead, not only to a reduced risk of HIV acquisition, but also to prompt recognition of seroconversion through regular HIV testing, thus decreasing the likelihood that an individual will go on to transmit HIV infection to others. FTC/TDF should be prescribed for the prevention of sexual acquisition of HIV infection in adults at high risk only as part of a comprehensive prevention strategy that emphasizes the importance of adherence to medication, screening for and treatment of other STIs, utilization of safer sex practices and regular HIV testing.

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KENDALL A MARCUS
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