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APPLICATION NUMBER:

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SUMMARY REVIEW

Decisional Review for NDA 21752/S-30

Date	July 16, 2012
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA #	NDA 21752/S-30
Supp #	
Proprietary / Established (USAN) names	Truvada [®] /emtricitabine (FTC) / tenofovir disoproxil fumarate (TDF)
Dosage forms / strength	200/300 mg in a fixed-dose combination, once daily
Proposed Indication(s)	For use in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk
Action	Approval

- 1. Introduction to Review:** This Division Director's memorandum provides an overview of NDA 21752/S-30 for Gilead Sciences' Supplemental New Drug Application (sNDA) for Truvada for pre-exposure prophylaxis (PrEP) in combination with safer sex practices for use in adults at high risk of acquiring HIV-1 infection. This decisional review highlights clinical trial results, PK/PD analyses used to support this indication, safety findings including resistance development, risk evaluation and mitigation strategies and post-marketing studies.
- 2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:** The HIV epidemic has affected tens of millions of people worldwide. A recent UNAIDS report¹ estimates that 34 million (31.6 – 35.2 million) people are living with HIV. Since the initial MMWR publication on June 5, 1981 where the first cases of AIDS were described, there have been up to 1.2 million HIV infections and almost 600,000 deaths domestically². At least since 2004, the incidence of HIV in the United States has remained stable at about 50,000³ new cases per year, despite condom availability, educational programs aimed at reaching high risk populations and effective treatment options. According to CDC, even though the annual incidence has been stable, there has been an estimated increase in certain subgroups, namely a 34% increase in young men who have sex with men (MSM). Further, among MSM aged 13-29, HIV incidence increased 48% among black/African American MSM from 2006-2009. Overall, the epidemic in the United States may be stable for most groups, but even this situation is unacceptable for a life-threatening disease.

¹ UNAIDS World AIDS Day Report, 2011

² CDC

³ Various sources: CDC, UNAIDS, Prejean et al, 2011, Hall et al, 2008

The 2010 National HIV/AIDS Strategy for the United States⁴ boldly endorsed multipronged approaches to HIV prevention. The following three principles of prevention are included in the 2010 National HIV/AIDS Strategy: 1) there must be a concerted effort to intensify HIV prevention efforts in communities where HIV is heavily concentrated, 2) targeted efforts must be expanded to prevent HIV infection using a combination of evidence-based approaches and 3) all Americans need to be educated about the threat of HIV and how to prevent it. If these principles are adopted, then anticipated results would be to lower new HIV infections by 25% by 2015 according to the report.

Further, CDC has published interim guidance⁵ on the use of Truvada in combination with safer sex practices for the prevention of HIV infection in MSM. This interim guidance followed the 2010 NEJM publication⁶ by Grant et al that described the results from the iPrEx trial that demonstrated that prevention efforts including use of Truvada once daily effectively decreased the risk of sexually-acquired HIV infection in MSM.

The sNDA for Truvada for a PrEP indication was submitted on December 14, 2011, and received on December 15, 2011. The application was granted a 6-month priority review because Truvada for PrEP demonstrated significant HIV risk reduction in clinical trials involving different populations and currently there are no approved drugs on the market for the prevention of HIV-1 infection. Truvada is the first drug(s) submitted for a PrEP indication. A major amendment addressing risk mitigation strategies was submitted in June 2012 that extended the review clock by three months.

Lastly, inspections of four clinical trial sites were conducted by the Division of Scientific Investigations (DSI). DSI determined that applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects were followed.

3. Chemistry/Manufacturing/Controls (CMC): This supplement is recommended for approval from the CMC perspective. Per Dr. Stephen Miller, there are no CMC issues.

4. Pharmacology/Toxicology: See review by Dr. Pritam Verma. Truvada has been marketed since 2004 and the individual components, TDF and FTC have been marketed since 2001 and 2003, respectively. Consequently, the adverse event profile in humans is well known. Both a reduction in bone

⁴ National HIV/AIDS Strategy for the United States, July 2010

⁵ MMWR, Interim Guidance: PrEP for the Prevention of HIV Infection in MSM, January 2011

⁶ Grant et al, NEJM, December 2010

mineral density and nephrotoxicity are important toxicities seen with Truvada. The package insert already contains wording related to these two areas based on nonclinical studies, the registrational trials that supported the treatment indication and post-marketing reports. For the prevention indication, Truvada should not be used if creatinine clearance is less than 60 mL/min. It is recommended that creatinine clearance and serum phosphorus be monitored in all individuals with mild renal impairment. If a decrease in creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, it is recommended that healthcare providers evaluate potential causes and re-assess potential risks and benefits of continued use. In prevention trials, bone fracture rates were similar between treatment and placebo groups. In addition, no increase in bone fracture rates was seen in treatment trials.

5. Clinical/Statistical including Clinical Pharmacology and Pharmacometrics:

Clinical pharmacology reviews were conducted by Drs. Shirley Seo and Ruben Ayala; pharmacometrics reviews were conducted by Drs. Yaning Wang and Jiang Liu. Clinical reviews were conducted by Drs. Kendall Marcus and Peter Miele; biostatistical reviews were conducted by Drs. Greg Soon and Tom Hammerstrom.

It is important to provide context as to why daily use of Truvada in combination with safer sex practices is being considered for a PrEP indication as opposed to TDF alone. From a regulatory perspective, under 21 CFR 300.50, two or more drugs may be combined in a single dosage form when each component makes a contribution and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling of the drug. It has been demonstrated that in vitro and in vivo data satisfy the regulations pertaining to combination drugs. The results of in vitro testing have shown that the combination of FTC and TDF results in additive to synergistic antiviral activity. In addition, Truvada showed greater efficacy than either of its component drugs in rectal challenge prevention studies in macaques. Further, the combination of FTC and TDF increases the genetic barrier to resistance and may therefore provide protection against transmission of viruses that are resistant to one of the component drugs. To further support the concept of a higher genetic barrier to resistance it was found, in a single-dose PK study examining intracellular tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) in HIV negative volunteers conducted by Anderson, et al, (University of Colorado, Denver) that intracellular concentrations of FTC-TP appear earlier than TFV-DP concentrations which may also help to prevent resistance. Lastly, clinical trials described below showed that Truvada in combination with safer sex practices was safe and efficacious.

CDC's Phase 2 trial 4323 was reviewed in support of safety. Datasets from Phase 3 studies, iPrEx and Partners PrEP were used to support safety and efficacy conclusions and PK/PD analyses. Pertinent findings from the thorough clinical/statistical and clinical pharmacology reviews of the iPrEx and Partners PrEP trials are described below. In addition, limited publicly available data from other prevention trials were reviewed (see Table 1).

CDC 4323, a phase 2 trial conducted in 400 U.S. MSM examined tenofovir compared to placebo plus other prevention services. The trial was designed to evaluate key safety parameters such as effects on bone (in a substudy conducted in 200 MSM in San Francisco) and kidney, in addition to behavioral risk compensation.

The iPrEx trial was a multicenter randomized, placebo-controlled trial sponsored by NIH's Division of AIDS examining use of Truvada plus condoms and counseling compared to placebo plus condoms and counseling in MSM at high risk of acquiring HIV infection. A total of 2499 subjects were enrolled: 1251 were randomized to the Truvada arm and 1248 were randomized to placebo.

A total of 131 seroconversion events occurred in the modified intention-to-treat (mITT) analysis population of 2442 randomized subjects (with at least one post-baseline HIV test, not HIV infected at enrollment minus 11 subjects who were ineligible): 48/1224 in the Truvada group and 83/1218 in the placebo group during the on-treatment period. Briefly, a regimen of once-daily Truvada in combination with safer sex practices demonstrated a 42% (95% CI 18-60) relative risk reduction in acquiring HIV infection. A pre-specified PK subgroup analysis was conducted to assess seroconversion rates based on adherence as measured by plasma TFV concentrations and intracellular (PBMC) concentrations of TFV-DP, a more reliable marker of adherence. Only 8% of seroconverters had detectable intracellular TFV-DP concentrations compared to 38% of non-seroconverters indicating that protection from seroconversion was associated with adherence, but overall adherence was low. Of note, self-reported adherence and adherence by pill count were unreliable. The FDA's advisory committee background document stated that high self-reported adherence was poorly predictive of measurable intracellular concentrations of the active forms of the Truvada components whereas low self-reported adherence was predictive of non-measurable drug concentrations.

FDA determined that estimated risk reduction among subjects with measurable intracellular drug concentrations approached 88% (95% CI 66-95%) when compared to placebo. While aligning with the tenet that those who adhered to the regimen had better outcomes, this was a post-randomization analysis that has the potential for bias and will not be included in labeling for

the following reasons: 1) since only 38% of non-seroconverters had detectable intracellular concentrations of TFV-DP, risk reduction of 88% may be an overestimate and 2) reduction of risk is multifactorial and may depend on the partner's viral load, condom use, sexual networks, STIs, etc. Of note, greater risk reduction was also seen in higher adherence subgroups including those with secondary or higher education, age greater than or equal to 25 years and reported unprotected anal intercourse at baseline.

Partners PrEP was a multicenter randomized, placebo-controlled three-arm trial of Truvada used daily plus condoms and counseling compared to tenofovir used daily plus condoms and counseling versus placebo plus condoms and counseling in 4758 serodiscordant couples in Kenya and Uganda sponsored by the University of Washington. The objective of this trial was prevention of acquisition of HIV-1 infection in the uninfected partner. A total of 82 seroconversions were reported among the three arms: 13, 17 and 52, respectively. Risk reduction for Truvada compared to placebo was 75% (95% CI 55-87%; $p < 0.001$). Risk reduction by gender demonstrated that Truvada was effective in men and women with an 84% risk reduction for men (95% CI 67-101; $p < 0.001$) and a 66% risk reduction for women (95% CI 41-92; $p = 0.005$). Further, FDA conducted sensitivity analyses to evaluate the impact of initiation of antiretroviral therapy in the infected index partners and study drug interruptions in female subjects who became pregnant or were breastfeeding; the sensitivity analyses support the overall conclusions.

FDA also conducted subgroup analyses examining the impact of adherence on study outcome. Case-cohort data were used from the Truvada arm of the Partners PrEP trial. Specifically, those subjects who had what was deemed never measurable plasma tenofovir levels had HIV seroconversion rates that were similar to placebo. Subjects whose plasma tenofovir levels were always measurable had the lowest rates of seroconversion of 0.1 per 100 person-years. The authors of the recently published trial results⁷ estimate that study medication was in use during 92% of the total follow-up time.

Top-line summaries from CDC's TDF2⁸ trial and publicly available abstracts from other completed or ongoing trials such as FEM-PrEP⁹ and VOICE¹⁰ were also reviewed. TDF2 was conducted in Botswana, a country with an HIV prevalence of 17.6% (2008), in heterosexual males and females considered to be at high risk. TDF2 was a phase 3 trial that compared Truvada to placebo each in combination with a prevention package of services including condoms. TDF2 was not powered to show a statistically significant effect on risk reduction by gender. Even though the trial closed early for futility as it was determined that more participants needed to enroll to maintain the power to

⁷ Baeten et al, NEJM, 2012

⁸ Thigpen, et al, NEJM, July 2012

⁹ Van Damme, et al, NEJM, July 2012

¹⁰ CROI 2012

identify a treatment effect, the overall results showed a risk reduction of 62% (95% CI 22-83).

The FEM-PrEP trial enrolled more than 2,000 high-risk women in Africa and was halted due to futility. There were approximately equal numbers of seroconversions in the Truvada and placebo arms. Potential explanations for this outcome include a perception by subjects that they were at low risk of acquiring HIV when they were actually at high risk and poor adherence as evidenced by the presence of detectable plasma drug concentrations > 10 ng/mL (a concentration considered as evidence that medication had been taken within 48 hours) in less than 26% of cases or controls. The VOICE trial in approximately 5,000 women also discontinued arms for futility based on DSMB recommendations. Namely, three arms were discontinued for futility – the oral TDF arm and tenofovir and placebo gel arms. The Truvada arm and matching placebo arm are continuing. Results are expected during the first quarter of 2013. Although the FEM-PrEP trial outcome is in contrast to iPrEx and Partners PrEP, prevention trial results overall illustrate the need for greater adherence. Further, there have been concerns that PrEP may be less effective in women than men. This was not the case in Partners PrEP as there was not a significant interaction between treatment effect and gender. In sum, several lines of evidence point to greater risk reduction with better adherence.

For completeness, summary data were also submitted from FHI PrEP and were used to support safety.

Table 1: Ongoing and Completed Trials of Oral Pre-exposure Prophylaxis

Trial	Sponsor	Location	Population	Intervention
Phase III, IIb				
iPrEx	NIH/DAIDS	Brazil, Ecuador, Peru, South Africa, Thailand, USA	Adult MSM at high risk	Daily oral FTC/TDF
Partners PrEP	University of Washington	Kenya, Uganda	Serodiscordant couples	Daily oral TDF or FTC/TDF
CDC TDF2	CDC	Botswana	Adult heterosexual men and women	Daily oral FTC/TDF
FEM-PrEP	FHI	Kenya, South Africa, Tanzania	Adult women at high risk	Daily oral FTC/TDF
VOICE	NIH/DAIDS	Uganda, South Africa, Zimbabwe	Adult women	Daily oral FTC/TDF or TDF or tenofovir vaginal gel
Phase II				
CDC 4323	CDC	USA	Adult MSM	Daily oral TDF (Immediate vs. delayed treatment)
FHI PrEP	FHI	Ghana, Cameroon, Nigeria	Adult women at high risk	Daily oral TDF

6. Clinical Virology: Please see extensive review by Drs. Jules O’Rear and Damon Deming. In iPrEx, Partners PrEP and CDC’s TDF2 trials, resistance was not seen in individuals who became infected after initiating Truvada during the trials, however resistance was seen in individuals who were infected but not detected at baseline and who received Truvada. Specifically, in iPrEx, two individuals receiving Truvada had unrecognized acute HIV infections at baseline and developed FTC-resistant viruses expressing M184V or M184I whereas 48 individuals who became infected while on Truvada did not develop resistant viruses. In Partners PrEP, one of the three individuals receiving Truvada who were infected at baseline developed FTC-resistant virus expressing M184V compared to 13 individuals who became infected after initiating Truvada and did not develop resistant viruses. In TDF2 an FTC- and TDF-resistant virus expressing A62V, K65R and M184V was detected in an individual who was infected at baseline while none of the 9 individuals who became infected while on Truvada developed resistance mutations.

Resistance is most likely to occur in individuals already infected at baseline. Therefore, before initiating PrEP, individuals need to be assessed for current or recent signs or symptoms consistent with acute HIV infection. As some acutely infected persons may be asymptomatic, individuals also need to be asked about potential exposure events such as condom breakage with an infected partner. This history will guide what

type of testing should be done. The following wording regarding testing appears in the label:

If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 seroconversion status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

The labeling further recommends that HIV-1 screening tests should be repeated at least every 3 months while using TRUVADA for a PrEP indication. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Even with a rigorous testing algorithm, resistance remains a concern. For the individual the development of viral resistance to FTC or TDF may impact future treatment options. On a population level, there is a possibility of transmission of resistant virus if Truvada for PrEP is used inconsistently.

Overall, we anticipate that the acquisition of resistance among PrEP users will occur infrequently. Individuals who consistently use once-daily TRUVADA for PrEP with safer sex practices and undergo regular testing are at a reduced risk for acquiring infection and are therefore unlikely to develop resistant virus. Those individuals who are infected and initiate PrEP may select for resistant virus as was seen in the trials. This scenario may also apply to intermittent users. Obviously those individuals who do not use the regimen may become infected but will not develop resistance due to lack of antiretroviral selective pressure.

In sum, the combination of counseling along with a detailed patient history, use of sensitive tests at baseline and screening tests at least every three months while using a daily PrEP regimen will help to reduce acquisition of HIV-1 infection and development of resistance.

- 7. Safety:** No new safety signals were seen in the PrEP trials, CDC4323, iPrEx, and Partners PrEP, though adherence was low in the iPrEx trial. CDC 4323 was conducted in 400 U.S. MSM who were randomized to receive a comprehensive prevention package of services in addition to TDF or placebo. In a BMD substudy, daily TDF resulted in a statistically significant reduction in BMD compared to placebo, but it is important to

note that there was a higher than expected prevalence of low BMD in this uninfected MSM population.

In iPrEx, moderate nausea (22 cases versus 10 cases) and unintended weight loss > 5% (34 cases versus 19 cases) were more commonly seen with Truvada as compared to placebo. Creatinine increases were mostly Grade 1. There were a total of 10 discontinuations (7 versus 3) for increases in creatinine and six of the seven individuals discontinuing Truvada for creatinine increases resumed Truvada without recurrence. In Partners PrEP, there were no statistically significant differences in key safety measures among treatment arms.

Grade 1 proteinuria (1+) occurred in 6% of subjects receiving TRUVADA in the iPrEx trial. Higher grades of proteinuria (2-4+) and glycosuria (3+) occurred in less than 1% of subjects treated with Truvada in the iPrEx and Partners PrEP trials.

Similarly for TDF2, no new safety concerns were identified with daily use of Truvada. Despite minimal but statistically significant BMD loss, fracture rates were low and comparable between Truvada and placebo.

Additional precautionary wording was included in labeling based on the PrEP indication. For example, the package insert states that TRUVADA for a PrEP indication should not be used in uninfected individuals with a creatinine clearance below 60 mL/min. A reduction in creatinine clearance from baseline should prompt a healthcare provider to evaluate the cause of the reduction and reassess the potential risks and benefits of continuing Truvada. There are no dose adjustments in the setting of renal insufficiency for the prophylaxis indication; Truvada should not be used in this setting. For both treatment and prevention, routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals with mild renal impairment [See *Warnings and Precautions (5.3)*].

Regarding effects on bone, the package insert already alerts health care professionals about this toxicity. From the prophylaxis studies as well as treatment trials, BMD changes appear to be reversible upon discontinuation of Truvada. With the PrEP indication, the following wording has been added to section 5.5:

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to -1.0% across total hip, spine, femoral neck, and trochanter in the TRUVADA group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving TRUVADA vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the

TRUVADA group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted [See Clinical Studies (14.2)]. The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial [See Clinical Studies (14.3)].

Development of viral resistance is also a safety issue for prophylaxis as it is for treatment. As previously discussed it could impact future treatment options. Labeling addresses measures to limit the development of seroconversion and resistance including wording stressing adherence; counseling, use of safer sex practices and use of sensitive HIV tests are also highlighted. In addition a REMS will be required to help to ensure appropriate use of Truvada for PrEP and post-marketing requirements to address resistance will be instituted and tracked (see below).

Risk compensation, as assessed by sexually transmitted infection (STI) rates and rates of self-reported condom usage and self-reported unprotected intercourse, for example, was not seen in iPrEx or in Partners PrEP. As previously mentioned, risk compensation was not seen in CDC4323. Further, in Dr. Miele's review, subjects reported a decrease in unprotected sex acts compared to baseline and STI incidence decreased compared to baseline.

The package insert already had a boxed warning regarding lactic acidosis and post-treatment exacerbation of hepatitis B. A warning not to prescribe or initiate PrEP until negative HIV-1 infection status has been confirmed was added to the box warning.

8. Risk Minimization Considerations and Post-marketing

Requirements/Commitments: FDA determined that a REMS was necessary for the safe use of Truvada for PrEP. A Medication Guide will also be part of labeling for Truvada for both treatment and prophylaxis. FDA did not institute a restrictive REMS, such as linking test results to a prescription as is the case with thalidomide because there would be difficulties in having two systems for dispensing Truvada for the two indications. A restrictive REMS that only applies to Truvada's prevention indication could be easily circumvented because Truvada and its individual components (FTC and TDF) are already available on the U.S. market for treatment of HIV. Further, a restrictive REMS for Truvada would have to apply to treatment as well as prevention. This could negatively impact access for HIV-infected patients who are taking Truvada for treatment and those individuals prescribed Truvada for post-exposure prophylaxis.

The central component of Truvada's REMS is a training and education program, as an element to assure safe use, directed to prescribers and other health care professionals to help educate uninfected individuals considering or taking Truvada for PrEP. Gilead Sciences must develop and implement these training and education programs, but they are not linked to access so that patients who need Truvada for PrEP or HIV treatment can get the medication. The REMS for Truvada for PrEP includes:

- a Medication Guide to educate uninfected individuals taking Truvada for PrEP about the serious risks of becoming infected with HIV, the potential for development of drug-resistant HIV-1 variants if they continue taking Truvada after becoming infected with HIV, and the importance of adherence along with safe sex practices.
- Prescriber training and education not linked to drug access that targets likely prescribers of Truvada for PrEP. This program includes:
 - A training guide for health care professionals that stresses the importance of the need for a negative HIV-1 test result before prescribing Truvada for PrEP, screening for sexually transmitted infections (STIs), adherence to the recommended dosing regimen and using Truvada for PrEP as part of a comprehensive prevention strategy that includes safer sex practices
 - A safety brochure for prescribers outlining key serious risk information about Truvada, the importance of comprehensive management with regular monitoring of HIV status and the importance of adherence to the dosing regimen

- A safety brochure for patients outlining key serious risk information about Truvada for PrEP, recommended screening tests before starting Truvada for PrEP, the importance of regular testing for HIV status while taking Truvada for PrEP, and key information to tell one's health care provider
- An education slide deck for face-to-face meetings between representatives of Gilead Sciences and prescribers
- A voluntary checklist for prescribers indicating they have taken the necessary steps to ensure the drug will be used appropriately that is to be placed in a patient's medical record
- A voluntary Prescriber-Individual Agreement Form to be signed by both parties and placed in a patient's medical record
- A journal information piece
- A Dear Healthcare Provider letter
- A safety information fact sheet

Evaluation of the REMS will take place annually from the initial date of approval.

In addition, multiple demonstration projects are being proposed by various investigators to evaluate use of Truvada for a PrEP indication and Gilead Sciences will be seeking access to the data from these projects. Some of these projects will provide information related to seroconversion including presence or absence of symptoms of acute retroviral syndrome, screening methods and resistance analyses in seroconverters. Others will provide information related to adherence via surveys and attitudes towards PrEP. We are also requiring data in pregnant women who choose to continue to use the product during their pregnancy.

The following Post-marketing requirements (PMRs) and commitments (PMCs) were requested:

PMRs

1906-1 Through collaboration with the Antiretroviral Pregnancy Registry, conduct a prospective observational study in order to collect and analyze data on maternal and fetal outcomes in 200 women who become pregnant while taking Truvada[®] for pre-exposure prophylaxis (PrEP) and choose to continue Truvada[®] during their pregnancies and in 200 women who become pregnant while taking Truvada[®] for PrEP and choose to discontinue it. Collect and analyze data from at least a similarly sized comparator group of pregnant HIV-infected women taking antivirals other than emtricitabine/tenofovir disoproxil fumarate. Data collected on pregnancy outcomes should include but not be limited to: timing of initiation and duration of Truvada[®] or other antiretrovirals, HIV seroconversions in mothers and infants, spontaneous and elective abortions, spontaneous and scheduled pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations.

Final Protocol Submission:	10/2012
Interim Report Submissions:	09/2013
	09/2014
	09/2015
	09/2016
Study Completion:	09/2016
Final Report Submission:	03/2017

1906-2 Collect and analyze data from individuals who take Truvada[®] for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who seroconvert during follow-up. The following data should be collected and the following analyses conducted on data collected from a minimum of 150 seroconverters over a time period not to exceed 3 years:

- Data regarding the presence or absence of signs and symptoms of acute HIV infection at the study visit or since the last study visit when seroconversion is identified.
- Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site.
- Analyses of baseline samples from early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.

- d. Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultrasensitive testing (such as ultra-deep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing.

This data may be collected from individuals participating in demonstration projects (trials).

Final Protocol Submission:	10/2012
Interim Report Submissions:	09/2013
	09/2014
	09/2015
Study Completion:	03/2016
Final Report Submission:	09/2016

- 1906-3 Conduct an analysis of data from ongoing and planned demonstration projects (trials) including at least 7000 uninfected individuals taking Truvada[®] for a pre-exposure prophylaxis (PrEP) indication with the objective of examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events. Levels of adherence should measure a gradient of adherence levels rather than the simple dichotomy of 'adherent' versus 'non-adherent' using any available data on drug levels as the measure of adherence. Seroconversion will be assessed every three months, and, upon each seroconversion, resistance testing should be performed. Assessment for renal and skeletal adverse events will be performed every three months, including evaluation of available laboratory data. Analyses will be performed by geographic region, including the United States.

Final Protocol Submission:	11/2012
Study Completion;	04/2016
Final Report Submission:	12/2016

PMCs

- 1906-4 Provide nationally representative drug utilization data to FDA of sufficient detail that use of Truvada[®] for a pre-exposure prophylaxis (PrEP) indication and individuals using Truvada[®] for a PrEP indication can both be characterized. These data should be submitted to FDA every 6 months for three years, for the combination product emtricitabine/tenofovir disoproxil fumarate, and for the single-ingredient products containing emtricitabine or tenofovir disoproxil fumarate, starting at one year following approval of the PrEP indication. The following analyses should be conducted with the data collected:

- 1) Total number of prescriptions dispensed across all settings of care
 - a. Total number of prescriptions dispensed, stratified by indication, setting of care, and prescriber specialty
 - b. Directions for use (signa) of prescriptions dispensed
- 2) Total number of unique patients receiving dispensed prescriptions across all settings of care
 - a. Total number of unique patients receiving dispensed prescriptions, stratified by both indication and setting of care
 - i. Unique incident users every quarter-year
 - ii. Unique prevalent users every quarter-year
 - b. Patient demographics of users of the product
 - c. Clinical characteristics of users of the product
- 3) Duration of therapy, including definitions of gaps in drug therapy
 - a. Total and stratified by indication
 - b. Examination of possible 'intermittent' use
 - c. Number of patients switching from PrEP to an HIV treatment regimen
 - d. Dose adjustments
- 4) Comparison of drug utilization data collected to data collected from demonstration projects (trials) performed in the United States in terms of patient demographics, patient clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

Final Protocol Submission:	01/2013
Interim Report Submissions:	07/2013
	01/2014
	07/2014
	01/2015
	07/2015
	01/2016
Final Report Submission:	07/2016

1906-5 In the context of a U.S. Centers for Disease Control and Prevention (CDC) demonstration project (trial) for once-daily Truvada[®] for a pre-exposure prophylaxis (PrEP) indication, validate an adherence questionnaire over the period of the demonstration project (trial) using an objective quantitative measure such as drug levels. In addition, the demonstration project (trial) will utilize subject demographics and responses from a survey on knowledge, attitudes, and behaviors (sexual and non-sexual behaviors related to increased risk of HIV

infection) in order to identify baseline characteristics associated with decreasing adherence, as measured via the adherence questionnaire and confirmed objectively by blood drug levels. The demonstration project (trial) will accrue 1200 individuals with an expected follow up of 12 months and use a national demographically representative sample that reflects the same target population described in 1906-4 above.

Final Protocol Submission:	04/2013
Study Completion:	07/2015
Final Report Submission:	02/2016

Clinical trials of Truvada for prevention of HIV-1 infection would be highly impracticable in a general pediatric population. Therefore, we are waiving the pediatric study requirement for this application for pediatric patients from birth to less than 16 years of age based on the incidence, prevalence rate, and route of transmission of HIV in this population.

8. Advisory Committee

This sNDA was presented before the Antiviral Products Advisory Committee on May 10, 2012. The committee was made up of experts in the areas of infectious diseases, public health, and risk mitigation.

Following presentations and discussion, advisory committee members were asked to vote on the following question related to the risk-benefit of Truvada in various populations. The specific voting question and results follow; transcripts will be made available at a later date:

Does the current application support a favorable risk-benefit assessment adequate to approve TRUVADA[®] for a PrEP indication in:

- a. **VOTE:** HIV-uninfected men who have sex with men (MSM)?
YES: 19 **NO: 3** **ABSTAIN: 0**

- b. **VOTE:** HIV-uninfected partners in serodiscordant couples?
YES: 19 **NO: 2** **ABSTAIN: 1**

- c. **VOTE:** Other individuals at risk for acquiring HIV through sexual activity?
YES: 12 **NO: 8** **ABSTAIN: 2**

Conclusions and Recommendations:

The HIV/AIDS epidemic continues. Though there has not been an increase in the incidence of new cases in the U.S. overall, certain populations continue to bear the impact of the epidemic. The number of new cases has remained stable in the U.S. at least since 2004. Although this may be reassuring for a less serious condition, it is disturbing for a serious and life-threatening disease such as HIV/AIDS.

Efficacy as measured by risk reduction in acquiring HIV infection was robustly demonstrated in iPrEx and Partners PrEP when daily Truvada was added to condoms and other safer sex practices compared to only condoms and safer sex practices. Results were not only replicated in two adequate and well-controlled clinical trials, but statistically significant outcomes were seen in different high risk populations, MSM and serodiscordant heterosexual couples. These trials and others examined the biological intervention of using an antiretroviral to prevent HIV-1 infection and correlated plasma and intracellular concentrations of the active moieties with outcomes, highlighting the importance of adherence.

Tenofovir and emtricitabine, nucleot(s)ides contained in Truvada have been marketed since 2001 and 2003, respectively and the fixed-dose combination, Truvada, has been on the market since 2004. Adverse effects of the individual components as well as the fixed-dose combination are well characterized and can be monitored. Wording has been added to the BOXED WARNING alerting patients and health care professionals that a negative HIV test must be confirmed before prescribing the drug and during usage. Detailed information has been added to the INDICATIONS AND USAGE section outlining factors that should be considered that place uninfected individuals at high risk for HIV acquisition. Truvada for PrEP has also been contraindicated in HIV-infected individuals or individuals with unknown HIV status to avoid the situation where PrEP would be inadvertently prescribed in the setting of acute HIV infection. Also, language has been added to the WARNINGS AND PRECAUTIONS section of the label to make it explicit that daily Truvada for PrEP should be used as part of a comprehensive management strategy to reduce the risk of acquiring HIV-1 infection and the importance of strict adherence to the dosing regimen.

Prescribers and potential users of Truvada must be made aware of symptoms of acute HIV infection to help guide testing and counseling before a prescription is written for Truvada for PrEP. With sensitive testing for HIV infection and an awareness of symptoms of acute HIV infection it is hoped that as few individuals as possible will be prescribed Truvada for a PrEP indication in the setting of acute HIV infection to avoid the potential for development of resistance. Even with a testing and counseling algorithm it is anticipated that resistance will be seen post-marketing. Our goal is to limit this situation.

Based on the safety and efficacy data submitted in the supplemental NDA and the informative package insert with Medication Guide and REMS, I am in full agreement with the multidisciplinary review team that Truvada for PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk should be approved. The totality of the data supports the conclusion that the benefits of Truvada for PrEP outweigh the risks. In addition, labeling and risk mitigation strategies will be utilized in an attempt to further diminish potential risks. Post-marketing requirements including demonstration projects examining resistance and post-marketing commitments address the concerns of the review team, consultants and the advisory committee.

Although the key trials only examined specific populations that included high risk MSM and serodiscordant couples, adults identified as being at high risk of sexually acquired HIV-1 infection could benefit from PrEP because all transmissions are inevitably in the setting of a discordant union. Although most of the data reviewed were obtained in non-US populations, FDA can accept foreign clinical trial data to support an application if the data can be applied to the US population, if labeling can adequately reflect the findings and if clinical trial sites pass inspection. Clearly this is the case for this indication.

Truvada for pre-exposure prophylaxis will supplement the current tools for HIV-1 prevention including safer sex practices such as condom use, risk reduction counseling and regular testing to determine HIV status. While the FDA can approve Truvada for prevention, other agencies, health care professionals and the indicated populations play an important role to ensure that it is used properly with condoms and other prevention services. The goals of this shared responsibility are to decrease the HIV incidence in the US, bring more at-risk persons into testing and treatment (if positive) and jump-start the possibility of future AIDS-free generations.

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