Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
May 10, 2012

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland

Topic: The committee discussed an efficacy supplement for new drug application (NDA) 21-752, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), submitted by Gilead Sciences, Inc. The supplemental application proposes an indication for Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.

These summary minutes for the May 10, 2012 meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration were approved on September 19, 2012.

I certify that I attended the May 10, 2012 meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Yvette Waples, Pharm.D.	Judith Feinberg, M.D.,FACP,FIDSA
Acting Designated Federal Officer, AVDAC	Acting Chairperson, AVDAC

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
May 10, 2012

The following is the final report of the Antiviral Drugs Advisory Committee meeting held on May 10, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Antiviral Products and posted on the Food and Drug Administration (FDA) website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm295937.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Antiviral Drugs Advisory Committee (AVDAC) of the FDA Center for Drug Evaluation and Research, met on May 10, 2012 at the FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Gilead Sciences, Inc. The meeting was called to order by Judith Feinberg, M.D., FACP, FIDSA (Acting Chairperson), and the conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Acting Designated Federal Officer). There were approximately 350 people in attendance. There were 37 Open Public Hearing speakers.

Issue: The committee discussed an efficacy supplement for new drug application (NDA) 21-752, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), submitted by Gilead Sciences, Inc. The supplemental application proposes an indication for Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.

Attendance:
AVDAC Members Present (Voting):
Amanda H. Corbett, Pharm.D.; Demetre C. Daskalakis, M.D., M.P.H.; Susan S. Ellenberg, Ph.D.; Thomas P. Giordano, M.D., M.P.H; Jeffrey S. Glenn, M.D., Ph.D.; Yoshihiko Murata, M.D., Ph.D.; Daniel Raymond (*Consumer Representative*); Doris B. Strader, M.D.; Russell B. Van Dyke, M.D.

AVDAC Members Not Present (Voting):
Elizabeth Connick, M.D.; Curt H. Hagedorn, M.D.; Karen Elizabeth Mark, M.D., M.P.H.; Barbara H. McGovern, M.D.

AVDAC Members Not Present (Non-voting):
Robin D. Isaacs, M.D. (*Industry Representative*)

Temporary Members (Voting):
Sally Blower, Ph.D.; Laura W. Cheever, M.D., ScM; Michelle M. Estrella, M.D., M.H.S.; Judith Feinberg, M.D., FACP, FIDSA (*Acting Chairperson*); Lawrence G. Hunsicker, M.D.; David T. Kuhar, M.D.; Elaine H. Morrato, Dr.PH., M.P.H., C.P.H.; Susan Newcomer, Ph.D.; Nancy S.

Padian, Ph.D., M.P.H.; Monica S. Ruiz, Ph.D., M.P.H.; Matthew V. Sharp (*Patient Representative*); Marlena Vega, MSW, Ph.D. (*Patient Representative*); Lauren V. Wood, M.D. (*Health Disparities Specialist*)

Acting Industry Representative to the Committee (Non-voting)
Patrick A. Robinson, M.D. (*Acting Industry Representative*)

Guest Speaker (Non-voting)
Susan Buchbinder, M.D.

CDC Speaker (Non-voting)
Lynn A. Paxton, M.D., M.P.H.

NIH Speaker (Non-voting)
Jeanna M. Piper, M.D.

FDA Participants (Non-voting):
Edward Cox, M.D., M.P.H.; Debra Birnkrant, M.D.; Jeffrey Murray, M.D., M.P.H.; Kendall A. Marcus, M.D.; Peter Miele, M.D.

Acting Designated Federal Officer:
Yvette Waples, Pharm.D.

Open Public Hearing Speakers:
Janet Leather, R.N.; Richard Elion, M.D. (Whitman Walker Health); Roxanne Cox-Iyamu, M.D.; Robert D. Elliott (AIDS Healthcare Foundation); Karen L. Haughey, R.N.; Archbishop Joyce Turner Keller (Aspirations); Miki Jackson; Joey Terrill (AIDS Healthcare Foundation); Tom Myers (AIDS Healthcare Foundation); Catherine Chien, M.D. (AIDS Healthcare Foundation); Christopher Lacharite, R.N., MSN, Ph.D.; Elizabeth "Liza" Nash, R.N., MPA, ACRN; Erika Aaron, MSN, CRNP; Herb Fisher; Kirk D. Myers (Abounding Prosperity, Inc.); Gerard Charles Kenslea; Matthew Rose; Jessie Gruttadauria; Wayne Chen, M.D. (AIDS Healthcare Foundation); Homayoon Khanlou, M.D. (AIDS Healthcare Foundation); Lindsey Dawson (The AIDS Institute); Mitchell Warren (AVAC: Global Advocacy for HIV Prevention); William Francis (Citywide Project, Inc.); Elizabeth McLendon (Episcopal Diocese of Upper South Carolina); Sal Guillen; Fannie M. Hudson, RNCM; Amy Pinter, R.N.; Rebecca Colon, D.O. (AIDS Healthcare Foundation Northpoint); Whitney Engeran-Cordova; Chris Collins (amfAR, The Foundation for AIDS Research); Monica Rutherford; Douglas M. Brooks, MSW (Justice Resource Institute); Omonigho Ufomata; Joanne Mayers; Michael Weinstein (AIDS Healthcare Foundation); Barry M. Rodwick, M. D., AAHIVS (AIDS Healthcare Foundation); Betina Kooima

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Judith Feinberg, M.D., FACP, FIDSA** Acting Chairperson, AVDAC
Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Acting Designated Federal Officer, AVDAC
Opening Remarks	**Debra Birnkrant, M.D.** Director, Division of Antiviral Products (DAVP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATION	
U.S. HIV Epidemiology and Risk	**Susan Buchbinder, M.D.** Director, HIV Research Section San Francisco Department of Public Health San Francisco, California
CDC PRESENTATION	
CDC PrEP Studies	**Lynn A. Paxton, M.D., M.P.H.** Captain, United States Public Health Service Medical Epidemiologist, Epidemiology Branch Division of HIV/AIDS Prevention Center for Disease Control and Prevention (CDC) Atlanta, Georgia
Clarifying Questions from Committee	
SPONSOR PRESENTATIONS	**Gilead Sciences, Inc.**
Truvada Overview	**Andrew Cheng, M.D., Ph.D.** Senior Vice President HIV Therapeutics & Development Operations Gilead Sciences, Inc.
Pre-Exposure Prophylaxis (PrEP) Initiative	**Robert M. Grant, M.D., M.P.H.** Senior Investigator, Gladstone Institute of Virology & Immunology Professor of Medicine University of California, San Francisco

Antiretroviral PrEP for HIV-1 Prevention Among Heterosexual Men and Women: the Partners PrEP Study	**Connie Celum, M.D., M.P.H.** Professor, Departments of Global Health and Medicine Adjunct Professor, Department of Epidemiology Director, International Clinical Research Center University of Washington **Jared Baeten, M.D., Ph.D.** Associate Professor, Departments of Global Health and Medicine Adjunct Associate Professor, Department of Epidemiology University of Washington
Truvada for PrEP	**Andrew Cheng, M.D., Ph.D.**
Closing Comments	**John W. Mellors, M.D.** Chief, Division of Infectious Diseases University of Pittsburgh

Clarifying Questions from Committee

BREAK

NIH PRESENTATION

VOICE Trial	**Jeanna M. Piper, M.D.** Senior Medical Officer, Division of AIDS National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) Bethesda, Maryland

FDA PRESENTATIONS

Truvada: Pre-exposure Prophylaxis (PrEP) Indication for Prevention of Sexually Acquired HIV-1	**Peter Miele, M.D.** Medical Officer DAVP, OAP, OND, CDER, FDA
Proposed Risk Evaluation and Mitigation Strategy (REMS) for Truvada for a Pre-exposure Prophylaxis (PrEP) Indication for Prevention of HIV-1 Infection	**Carolyn L. Yancey, M.D.** Medical Officer Division of Risk Management Office of Medication Error Prevention and Risk Management Office of Surveillance and Epidemiology (OSE) CDER, FDA

Clarifying Questions from the Committee

LUNCH

Open Public Hearing

BREAK

Charge to the Committee **Debra Birnkrant, M.D.**

Questions to the Committee and Committee Discussion

ADJOURNMENT

Questions to the Advisory Committee:

1. 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***

   If no, what additional data are needed to support a favorable risk-benefit assessment adequate to approve TRUVADA for this indication for the populations listed above?

   If yes, please address the following topics *(questions #2 through #5)*:

   Committee Discussion: *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 (question #1a) and in HIV-uninfected partners in serodiscordant couples (question #1b). Those who voted "Yes" stated that there was positive efficacy data demonstrated in both HIV-uninfected MSM and HIV-uninfected partners in serodiscordant couples. It was emphasized that TRUVADA® for a PrEP indication should be part of a package of prevention strategies offered by the prescriber. Those who voted "No" noted concerns with placing patients at undue risk and they also expressed that there was not sufficient efficacy data because there was a limited number of African American MSM subjects and lack of African American female representation in the trials. For question #1c, more than half of the committee members 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. Those who voted "Yes" agreed that the benefit is greater than the risk. Those who voted "No" or abstained stated that there is inadequate data for this indication.

There was a general consensus 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. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss laboratory testing during administration of TRUVADA for a PrEP indication.

   a. How frequently should HIV testing be recommended?

      Committee Discussion: *There was a general consensus that baseline HIV testing is crucial. A two to four month frequency for repeat testing was recommended.*

   b. Which safety assessments should be recommended and how frequently?

      Committee Discussion: *Committee members recommended the following safety assessments:*

      - *Hepatitis B virus testing at baseline. There would be an opportunity to vaccinate susceptible patients.*
      - *Baseline renal function test and frequent monitoring of renal function, particularly monitoring for evidence of proximal tubulopathy for which routine monitoring of renal function is insensitive. It was recommended that testing be performed more often in patients with risk factors for kidney disease such as diabetes, hypertension, hepatitis C, injection drug use and others at high risk of kidney disease such as African-Americans.*
      - *Testing for sexually transmitted infections (STIs) because of the increased risk of HIV acquisition in the presence on untreated STIs.*
      - *Baseline bone mineral density test for those at increased risk, and routine interval monitoring.*
      - *Monitoring for drug resistance, which may be facilitated by having a checkbox for "PrEP" on test requisitions.*

   Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Please comment on the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS).

   a. Prescriber education program including appropriate target prescribers.

      Committee Discussion: *The vast majority of committee members stated that a negative HIV test should be a requirement before prescribing TRUVADA® for PrEP. The Agency stated that such a requirement would essentially result in restricted distribution*

negatively impacting the availability of TRUVADA® for both treatment and prevention. The Agency provided reasons for why 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 (physicians and mid-level practitioners) and consumers. Recommendations include:

- *Creating a checklist and/or contract between provider and consumer detailing the expectations of each.*
- *Involving the community in creating materials for patients and physicians.*
- *Utilizing interpersonal communication by having community advocacy groups, organizations, and professional societies serve as educators, mentors and role models.*
- *Incorporating testimonials in education programs and marketing tools.*
- *Educating non-HIV health care providers on how to recognize the symptoms of acute HIV (seroconversion syndrome).*
- *Continuing education (CE) programs to attract targeted groups of healthcare providers who are not experienced providers of HIV care.*
- *Creating effective social marketing campaigns to educate patients.*

b. What metrics could be considered in the REMS assessment in addition to prescriber and user surveys, number of prescribers trained and drug usage data?

Committee Discussion: *The committee recommended that the REMS assessment be proactive and aggressive. There was considerable concern that the proposed REMS was too passive and would not result in healthcare provider behavior change needed to ensure safe use of TRUVADA® for PrEP, particularly for resistance development and toxicity. The following metrics in the REMS assessment were recommended:*

- *Create a method to capture data on how many prescriptions are written for TRUVADA® for the PrEP indication.*
- *Obtain data on the appropriateness of prescriptions for TRUVADA® for the PrEP indication. Physician registries were recommended to capture this data.*
- *Create a means of capturing non-adherence, including reasons for non-adherence and/or discontinuation of drug.*
- *Assess each point in the CDC interim guidance on HIV PrEP in MSM.*

Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** What postmarketing studies should be conducted (e.g. emergence of drug resistance, behavioral changes, patterns of use, safety assessments)?

Due to time limitations, question #4 was not addressed.

5. **DISCUSSION:** Please comment on whether the currently available evidence on the efficacy of TRUVADA for a PrEP indication make the conduct of placebo-controlled trials of primary HIV prevention unethical.

   Due to time limitations, question #5 was not addressed.

The meeting was adjourned at approximately 8:30 p.m.