Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
May 11, 2012

Location: DoubleTree Hotel by Hilton Washington D/C, Silver Spring, 8727 Colesville Road, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 203100, for a fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, submitted by Gilead Sciences, Inc. The application proposes an indication for the treatment of HIV-1 infection in adults who are antiretroviral naïve or have no known substitutions associated with resistance to the individual components.

These summary minutes for the May 11, 2012 Meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration were approved on June 22, 2012.

I certify that I attended the May 11, 2012 meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**/s/**_____
Yvette Waples, Pharm.D.
(Acting Designated Federal Officer, AVDAC)

_____**/s/**_____
Yoshihiko Murata, M.D., Ph.D.
(Acting Chair, AVDAC)

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
May 11, 2012

The following is a final report of the Antiviral Drugs Advisory Committee meeting held on May 11, 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 11, 2012 at the DoubleTree Hotel by Hilton Washington D/C, Silver Spring, 8727 Colesville Road, 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 Yoshihiko Murata, M.D., Ph.D. (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 150 people in attendance. There were three Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 203100, for a fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, submitted by Gilead Sciences, Inc. The application proposes an indication for the treatment of HIV-1 infection in adults who are antiretroviral naïve or have no known substitutions associated with resistance to the individual components.

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. (*Acting Chairperson*); Daniel Raymond *(Consumer Representative)*; Doris B. Strader, 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.; Russell B. Van Dyke, M.D.

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

Temporary Members (Voting):
Laura W. Cheever, M.D., ScM; Michelle M. Estrella, M.D., M.H.S.; Lawrence G. Hunsicker, M.D.; David T. Kuhar, M.D.; 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)*

FDA Participants (Non-voting):
Edward Cox, M.D., M.P.H.; Debra Birnkrant, M.D.; Jeffrey Murray, M.D., M.P.H.; Linda Lewis, M.D.; Adam Sherwat, M.D.

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

Open Public Hearing Speaker:
Lynda Dee; James Driscoll, Ph.D. (AIDS Healthcare Foundation); Jason King (AIDS Healthcare Foundation)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Yoshihiko Murata, M.D., Ph.D.** Acting Chairperson, AVDAC
Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Acting Designated Federal Officer, AVDAC
Opening Remarks	**Linda Lewis, M.D.** Medical Team Leader Division of Antiviral Products (DAVP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Gilead Sciences, Inc.**
Introduction	**Andrew Cheng, M.D., Ph.D** Senior Vice President Clinical Research and Development Operations Gilead Sciences, Inc.
Early Clinical Development	**Brian Kearney, Pharm.D.** Senior Director Clinical Pharmacology Gilead Sciences, Inc.
Clinical Program, Efficacy and Safety	**Javier Szwarcberg, M.D., MPH** Senior Director Clinical Research Gilead Sciences, Inc.
Benefit/Risk	**Andrew Cheng, M.D., Ph.D.**

Clarifying Questions from Committee

BREAK

FDA PRESENTATION

Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF) Fixed Dose Combination	**Adam Sherwat, M.D.** Medical Officer DAVP, OAP, OND, CDER, FDA

Clarifying Questions from the Committee

LUNCH

Open Public Hearing

Charge to the Committee	**Linda Lewis, M.D.**

Questions to the Committee and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion

ADJOURNMENT

Questions to the Advisory Committee:

1. **DISCUSSION:** Please comment on the safety profile of elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate, focusing on proximal tubulopathy and other renal adverse events leading to subject discontinuation.

   Committee Discussion: *Overall, the committee was concerned with the limitations of the current study data and recommended longer term follow-up and additional studies to address renal abnormalities and drug-drug interactions with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) use.*

   Additional recommendations included:

   - *Education for prescribers on tubulopathy, specifically on the various tests that are available (e.g., urine protein, urine glucose, serum creatinine, and calculated creatinine clearance) and how to analyze renal laboratory data in efforts to detect potential tubulopathy early. The possible use of less widely available tests to assess for tubulopathy (e.g., B2-microglobulin) was also discussed.*

- *The use of the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) to measure kidney function. It was noted that this formula has the least bias in the normal range but is not well validated in HIV-positive patients. Alternative methods to estimate GFR (e.g., use of cystatin C) were also discussed.*
- *Heightened vigilance in patients that have known risk factors for renal disease (i.e. diabetes, hypertension, family history).*
- *Further studies on the safety profile of EVG/COBI/FTC/TDF use in women.*

Please see the transcript for details of the committee discussion.

2. **VOTE:** Considering the overall risks and benefits, do the available data support approval of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults?

   YES: 13 ***NO: 1*** ***ABSTAIN: 0***

   a. If no, what additional studies are recommended?

   b. If yes, proceed with the remaining questions *(questions #3 and #4)*:

   Committee Discussion: *The majority of the committee agreed that the available data support approval of EVG/COBI/FTC/TDF as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults. Those who voted "Yes" stated that there was positive efficacy data demonstrated and a favorable risk-benefit profile with EVG/COBI/FTC/TDF use. The panel member who voted "No" expressed concerns relating to the EVG/COBI/FTC/TDF potential effects on kidney function and the limited amount of data involving women participating in the clinical trials to date. In addition, the panel member noted that there are alternatives to EVG/COBI/FTC/TDF available for treatment of HIV-1 infection in treatment-naïve adults and recommended that the Agency wait to make a decision on approval until the ongoing studies on EVG/COBI/FTC/TDF are complete. Overall, the committee stressed the need for further studies. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Please comment on whether there are additional measures needed to improve renal safety in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. As part of your discussion, please comment on the following:

   a. Would additional laboratory monitoring (e.g., urine dipstick testing for protein and glucose) potentially improve renal safety? Does use in patients with baseline glycosuria and proteinuria warrant separate recommendations?

      Committee Discussion: *Overall, the committee agreed that additional laboratory monitoring would potentially improve renal safety. There was general agreement that urine dipstick testing would be inexpensive, simple to perform, and would not constitute a burden to practicing physicians. It was noted that other modalities, such as baseline protein quantification (via a 24 hour urine collection) and monitoring of patients' urine*

protein-creatinine ratio, might be helpful. There was no specific discussion related to the use of E/C/F/T in patients with baseline glycosuria and proteinuria. Please see the transcript for details of the committee discussion.

b. Would renal safety be enhanced by monitoring renal function in all patients as opposed to only patients with renal impairment or at risk of renal impairment?

Committee Discussion: *The committee agreed that additional monitoring would potentially improve renal safety, and that renal safety would be enhanced by monitoring renal function in all patients as opposed to only patients with renal impairment or at risk for renal impairment. Please see the transcript for details of the committee discussion.*

c. Should laboratory cutoffs be provided to help distinguish the effect of cobicistat on serum creatinine and creatinine clearance from genuine renal dysfunction? If yes, please comment on specific parameters, including, but not limited to the Applicant's current proposal.

Committee Discussion: *Overall, the committee agreed that there should be laboratory cutoffs provided to help distinguish the effect of cobicistat on serum creatinine and creatinine clearance from genuine renal dysfunction. There was general agreement with the Applicant and Agency's suggestion of using a confirmed serum creatinine increase of greater than or equal to 0.4 mg/dL from baseline. One of the renal experts on the panel also suggested the use of percent increase in serum creatinine as an adjunctive measure.*

4. **DISCUSSION:** Please discuss any post marketing studies needed to further define risks or optimal use of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

Committee Discussion: *The committee recommended post marketing studies be conducted to address the following:*

- *EVG/COBI/FTC/TDF use in women*
- *Longer-term safety monitoring focusing on renal and bone parameters*
- *Alternate methods and optimal markers for early detection of tubulopathy and appropriate timing of monitoring*
- *Pharmacodynamic/pharmacokinetic interactions between PK enhancers (e.g., COBI) and tenofovir*
- *Drug-drug interactions (e.g., antiretrovirals for "salvage therapy," hepatitis C protease inhibitors, oral contraceptives, methadone)*
- *Drug resistance, including but not limited to the development of resistance to HIV protease inhibitors associated with the use of COBI.*
- *Metabolic profile changes while on therapy*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 3:00 p.m.