1 FOOD AND DRUG ADMINISTRATION

2 CENTER FOR DRUG EVALUATION AND RESEARCH

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5 ANTIVIRAL DRUGS ADVISORY COMMITTEE

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8 FRIDAY, MAY 11, 2012

9 8:00 a.m. to 3:00 p.m.

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13 DoubleTree by Hilton

14 Washington DC/Silver Spring

15 8727 Colesville Road

16 Silver Spring, Maryland

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. WAPLES: Good morning, everyone. I would like to first remind everyone to please silence your cell phones, BlackBerry, other devices if you have not already done so. I would like to identify the FDA press contact, Stephanie Yao. If you're present, please stand. Thank you.

Call to Order

Introduction of Committee

DR. MURATA: Good morning. My name is Yoshi Murata. I'm the acting chair of the Antiviral Drug Advisory Committee for today. I hope that those of us who were here yesterday had the chance to rest, and this is day 2 of the doubleheader.

I will now call the meeting to order. We will go around the room, and please introduce yourself. We will start with the FDA and Dr. Edward Cox to my left, and we'll go around the table.

DR. COX: Good morning. Ed Cox, director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debbie Birnkrant, division director, Division of Antiviral Products.

DR. MURRAY: Jeff Murray, deputy director, Division of Antiviral Products.

DR. LEWIS: Linda Lewis, medical team leader, Division of Antiviral Products.

DR. SHERWAT: Adam Sherwat, medical officer, Division of Antiviral Products.

DR. ESTRELLA: Michelle Estrella, nephrologist from Johns Hopkins.

DR. HUNSICKER: Larry Hunsicker, kidney doctor from the University of Iowa, clinical trialist.

DR. VEGA: Marlena Vega, executive director of A Will to Live, and here I am a patient advocate. This hat is on.

DR. WOOD: Good morning. Dr. Lauren Wood, I'm a senior clinical investigator at the National Cancer Institute in Bethesda. My expertise is pediatric infectious disease, internal medicine, and allergy and immunology.

DR. GIORDANO: Good morning. I'm Tom

Giordano. I'm at Baylor College of Medicine in the Michael DeBakey VA in Houston, and I'm an infectious disease physician and HIV researcher.

DR. MURATA: Yoshi Murata, infectious diseases, University of Rochester School of Medicine and Dentistry.

DR. WAPLES: Yvette Waples, I'm the acting designated federal officer for this meeting.

DR. STRADER: Doris Strader, Division of Gastroenterology and Hepatology, Fletcher Allen University of Vermont.

DR. GLEN: Jeffrey Glen, Division of Gastroenterology and Hepatology, Stanford University.

DR. DASKALAKIS: Demetre Daskalakis, Division of Infectious Diseases, New York University School of Medicine, Bellevue Hospital.

MR. RAYMOND: Good morning. Daniel Raymond, policy director, Harm Reduction Coalition, New York.

DR. ELLENBERG: Susan Ellenberg, biostatistician, University of Pennsylvania.

DR. CORBETT: Hello, I'm Amanda Corbett, clinical associate professor at the University of North Carolina.

DR. KUHAR: Hi. I'm David Kuhar. I'm an infectious diseases physician, and I'm with the Centers for Disease Control and Prevention.

DR. CHEEVER: Laura Cheever. I'm an infectious disease physician as well. I'm chief medical officer and deputy of the HIV/AIDS bureau at the Health Resources and Services Administration.

DR. ROBINSON: I'm Patrick Robinson. I'm substituting today as the industry representative, and I'm with Boehringer Ingelheim.

DR. MURATA: So for topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus as a gentle reminder, individuals will be allowed to speak into

the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Yvette Waples, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. WAPLES: The Food and Drug Administration, FDA, is convening today's meeting of the Antiviral Drugs Advisory Committee under the

authority of Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a

particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today the committee will discuss a new drug application, NDA 203100, for a fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir

disoproxil fumarate submitted by Gilead Sciences, Incorporated.

The application proposes an indication for the treatment of HIV-1 infection in adults who are antiretroviral naive or have no substitution associated with resistance to the individual components.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Patrick Robinson is participating in this meeting as a nonvoting representative, acting on behalf of regulated industry. Dr. Robinson's role at this meeting is to represent industry in general and not any particular company. Dr. Robinson is

employed by Boehringer Ingelheim Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals is a producer of two antiretroviral agents.

We would like to remind members and temporary voting members that if the discussion involves any other products or forms not already on the agenda for which an FDA participant has a personal or imputed financial interest, that participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. MURATA: Thank you, Ms. Waples.

We will now proceed with the FDA opening remarks from Dr. Linda Lewis.

Opening Remarks – Linda Lewis

DR. LEWIS: Good morning. Well, after yesterday's marathon meeting that was productive, I am really happy to see all of our advisory

committee members here again bright eyed and ready to go.

Today I'd like to welcome you to the advisory committee meeting to consider the application for elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as a fixed-dose combination tablet. This application is submitted by Gilead Sciences.

Today my job is to set the stage for the presentations you will hear by Gilead and the FDA staff. Over the next few minutes, I'll give you some background on the product and highlight some of the unique regulatory aspects of this application. In addition, I will outline the aspects that we and the applicant believe are the most important clinical topics to be discussed in the presentations, the issues we wish the committee to discuss, and provide a skeleton agenda for the rest of the day.

This product – and I'm going to call it E/C/F/T, and that's what the FDA presentations will call it; the company may call it the QUAD pill

because it's a mouthful to get through – is a complete regimen intended for treatment of HIV infection in treatment-naive adults.

This new fixed-dose combination product, or FDC, contains two new and two approved products. Elvitegravir is a new integrated strand transfer inhibitor and represents only the second drug in this class.

Cobicistat is a new mechanism-based pharmaco-enhancer. In this fixed-dose combination tablet, it functions to increase elvitegravir exposure by virtue of its activity as a CYP3A4 inhibitor. Cobicistat is the first product to be developed and submitted in an NDA solely as a PK booster for another product.

Emtricitabine and tenofovir are approved as individual drugs and as part of other FDCs. Together, they represent the most widely prescribed NRTI backbone of antiretroviral therapy regimens and are recommended in HHS treatment guidelines preferred regimens.

I'll just refresh your memory a little bit

about drug development for HIV. Since 1987, the FDA has approved 26 distinct antiretroviral drug products for the treatment of HIV falling into six different drug classes. Drug development during this time has allowed the standard treatment recommendations to evolve from single drug or monotherapy to combinations of NRTI therapy, to highly active antiretroviral therapy using NRTIs in combination with protease inhibitors or NNRTIs, and later with entry inhibitor CCR5 antagonists, and finally, integrase inhibitors.

Over the last 15 years, several two-drug and three-drug fixed-dose combination products of NRTIs and NNRTIs have been approved, as you can see in the red highlights.

The E/C/F/T fixed-dose combination tablet NDA has a number of unique regulatory aspects. As I noted in a previous slide, there are currently six approved FDCs. The first of the complete regimen FDCs was Trizivir. It comprised of three NRTIs and is no longer really considered optimal therapy for HIV and is rarely used.

Atripla, containing efavirenz in combination with tenofovir, efavirenz, was the first FDC containing both NRTI and NNRTI drug classes. At the time of its approval, it was hailed as the one drug once a day, one pill once a day, and rapidly became one of the most popular regimens in patients initiating antiretroviral therapy. More recently, Complera, also an NRTI, NNRTI combination, was approved.

Three NRTI combination FDCs, Combivir, Epzicom and Truvada, were also approved and can be combined with any of the other classes of drugs. However, all of the currently available FDCs were approved on the basis of bioequivalence of the FDC compared to the individual component drugs taken together. They were all approved after the approval of the individual component drugs.

The E/C/F/T FDC submitted for review has been submitted prior to the submission of the elvitegravir and cobicistat single drug NDAs. Because the earlier FDCs were approved on the basis of bioequivalence studies, this is the first time

an FDC containing new drugs has been reviewed by this advisory committee.

The E/C/F/T fixed-dose combination development program is linked to but independent of the results of the elvitegravir and cobicistat single drug efficacy trials. The doses of elvitegravir and cobicistat for use in the FDC were selected based on data from these single drug development programs. But this FDC NDA is supported by data from two adequate and well-controlled clinical trials of the FDC compared to HHS preferred regimens; in one case, Atripla in Gilead Study 236-0102 and in the other study compared to Truvada plus boosted atazanavir, Study 236-0103.

The applicant has also submitted all relevant nonclinical studies of both elvitegravir and cobicistat and clinical pharmacology studies related to both the individual drugs and the E/C/F/T combination product.

Finally, some additional safety data from the individual elvitegravir and cobicistat

development programs has been provided. It is important to note that the advisory committee will not be asked to evaluate the merits of elvitegravir and cobicistat as single products.

This morning, you will hear presentations from Gilead Sciences and from the Division of Antiviral Products. The applicant will provide an overview of the early development of the fixed-dose combination and the basis for dose selection. You will hear both groups summarize the efficacy of E/C/F/T fixed-dose combination compared to Atripla and the Truvada plus boosted atazanavir.

The presentations will describe the data regarding emergence of resistance to elvitegravir and other antiretroviral drugs. The presenters will discuss the clinical pharmacology of the FDC, including both identified and expected drug-drug interactions.

Also, the presentations will summarize the safety profile of E/C/F/T in comparison to the two other regimens, focusing on common adverse events, serious adverse events, laboratory monitoring and

bone toxicity. A particular focus of the safety summaries will be the occurrence of serious renal adverse events, including proximal tubulopathy and proposals for monitoring that event.

Just one disclaimer, the FDA reviews are still in progress, and the presentations today represent our team's preliminary findings. Reviews from all disciplines and inspections of manufacturing facilities must be completed satisfactorily before any regulatory action can be taken.

The issues for the committee's discussion will come after the presentations, and we expect you to provide input on a number of different topics. Most important to us is the committee's assessment of the safety profile and risk/benefit of E/C/F/T as a fixed-dose combination in this population. Do the available data support approval of E/C/F/T fixed-dose combination in treatment-naive patients?

We will ask the committee to discuss the most appropriate approach for monitoring renal

toxicity. And finally, if approved, are additional postmarketing studies needed?

The agenda has changed slightly since the program was initially was published, and I've included a copy here, but you-all should have gotten an updated copy as you came in.

I'd like to thank the advisory committee in advance for your work today. We look forward to a lively discussion, and we appreciate insightful advice. Thank you.

DR. MURATA: Thank you, Dr. Lewis.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the

firm at issue, such as consulting fees, travel expenses, honoraria and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation – Andrew Cheng

DR. CHENG: Good morning. My name is Andrew Cheng. I am the leader of the HIV therapeutics and development operations group at Gilead. On behalf of Gilead Sciences, I'd like to thank the committee and the FDA for this opportunity to present our data supporting the use of elvitegravir/cobicistat/emtricitabine/tenofovir DF, hereafter referred to as QUAD, for the treatment of

HIV-1 infection in adults.

Despite the great progress that we've made in the treatment of HIV, there still remains challenges. As we heard yesterday, there are roughly 1.2 million HIV-infected individuals in the United States. Approximately 750,000 of these individuals are not receiving antiretroviral therapy.

Over time, you can see, on the bottom of this slide, that the treatment guidelines have evolved where as of March of this year, the Department of Health and Human Services treatment guidelines advise treatment for all HIV-infected individuals independent of CD4 cell count.

Currently, as indicated by Dr. Lewis, there are three preferred regimen classes. There are non-nucleoside inhibitor-based regimens, protease inhibitor-based regimens, and integrase-based regimens for four preferred regimens. Overall, all of these are supported by the nucleoside backbone of emtricitabine and tenofovir DF, and all but the integrase class are once daily regimens.

Each of these regimens are the preferred regimens, however, there are some limitations. With the Atripla, the efavirenz-based single tablet regimen, there are commonly known central nervous system adverse events, rash. It's a pregnancy category D drug because of its teratogenic potential and its inability to combat transmitted non-nucleoside resistance, which, depending on the community in the United States, ranges anywhere from 8 to 15 percent of patients in a community.

When one looks at the protease inhibitor-based regimens, on the left-hand side, there are some limitations that include pill burden and some other protease inhibitor-related limitations. And then on the right-hand side, there are some specific limitations, such as hyperbilirubinemia that are associated with boosted atazanavir.

The integrase-based regimen, raltegravir, as noted earlier, is a twice-daily regimen, and the only regimen that is twice daily in the preferred guidelines class.

1 These limitations create the need for new
2 treatment options, which should provide consistent
3 and potent efficacy, activity against transmitted
4 non-nucleoside resistance, a favorable safety
5 profile which is well-tolerated, and a once-daily
6 regimen, ideally, a single tablet regimen, as these
7 regimens have shown to be popular in the United
8 States.
9 In addition, they provide important benefits
10 when it comes to all or none therapy.
11 Specifically, it prevents the use of selective
12 adherence, that is, taking only some components of
13 a regimen. The regimen is taken all or none; and
14 lastly, a pregnancy category B drug.
15 In order to accomplish these goals, QUAD
16 combines four components. On the left, there are
17 the two components, emtricitabine and tenofovir,
18 which are already approved in a number of
19 fixed-dose combination tablets, most notably as
20 Truvada, which we discussed yesterday.
21 There's a long regulatory history with
22 tenofovir and emtricitabine as tenofovir has been

approved for roughly 11 years with approximately 9 million patient years of experience. Emtricitabine, approved in 2003, has roughly 4 million patient years of experience.

On the right, there are two new drugs in this combination, elvitegravir, which is an integrase strand transfer inhibitor, the second agent to be considered in this class for approval. It is once daily, one boosted by cobicistat, and it is active against non-nucleoside resistant HIV.

Cobicistat is a mechanism-based cytokine 3A4 inhibitor which does not have anti-HIV activity, which also means that it does not select for resistance.

The QUAD tablet is a bilayer. There are two layers. The bottom layer is the elvitegravir/cobicistat layer, roughly 700 milligrams, and on the top is the Truvada layer, which is roughly 650 milligrams. In comparison to the available single tablet regimens, once-daily single tablet regimens, you see on the right-hand side, it is in between the size of Atripla and

Complera. That is, it is 1.35 grams.

Our proposed indication for the QUAD tablet is as follows: it is a complete regimen for the treatment of HIV-1 infection in adults who are treatment-naive or have no known substitutions with resistance to the individual components.

In today's presentation, Dr. Brian Kearney will speak to the early clinical development and dose selection of the individual components of elvitegravir and cobicistat, followed by Dr. Javier Szwarcberg who will speak to the efficacy and safety in Studies 102 and 103 as well as the renal safety analysis and recommendations. And I will conclude with the benefit/risk.

At this point, I'd like to ask Dr. Kearney to come to the podium.

Sponsor Presentation – Brian Kearney

DR. KEARNEY: Good morning. My name is Brian Kearney, and I head up the clinical pharmacology group at Gilead Sciences.

As Dr. Cheng mentioned, this morning, it's my pleasure to walk you through the early clinical

development of QUAD, specifically that of the two new chemical entities contained within, elvitegravir, the antiretroviral, and cobicistat, the booster.

I'll share with you the antiretroviral activity of the compound of elvitegravir as well as its PK profile and why we decided to develop it as a boosted drug, and then I'll walk you through pharmacokinetic and pharmacodynamic assessments that led to the 150-milligram dose selection.

For cobicistat, I'll share with you the data that led to its discovery and development and eventual selection as it moved into the clinic and the pharmacodynamic assessments we conducted with it that led to its 150 milligram dose selection.

I'll share with you data when we identified an unexpected effect of cobicistat on increasing serum creatinine in decreasing estimated GFR and its characterization.

I'll also share with you some data on tenofovir exposure in HIV-infected patients who received the QUAD, that tenofovir is the

p glycoprotein substrate, and cobicistat like ritonavir can inhibit p glycoprotein during the absorption of tenofovir and result in slightly higher systemic exposures.

At the end of my presentation, I'll share with you some PK/PD analyses from patients in our phase 2 and phase 3 program with QUAD that confirmed dose selections of both elvitegravir and cobicistat. And then I'll share with you some data as it relates to important drug-drug interactions in terms of managing your patients who will be receiving the QUAD.

So by way of background, HIV integrase is a viral enzyme that's essential for viral replication. It inserts the viral genome into the host DNA. As has been previously mentioned, elvitegravir similar to raltegravir is an integrase strand transfer inhibitor.

Elvitegravir is a potent compound with a protein binding adjusted IC95 of 45 nanograms per mil. This number is important as this – as our desire is to maintain antiviral activity over the

dosing interval in all patients. And as you'd expect as an integrase inhibitor, is active against viruses that develop resistance to the other compounds, the other classes of compounds to treat HIV.

This cartoon depicts the metabolism of elvitegravir. Elvitegravir entered clinical development at Gilead in 2005, and we knew from preclinical data that it was predominantly metabolized by CYP3A and by a lesser extent by glucuronidation.

As such, we knew during its development, it would be co-administered with a ritonavir boosted PI regimens and as such needed to understand the drug-drug interaction potential. More than that, though, we wanted to understand whether boosted administration of elvitegravir being a CYP3A substrate may offer an optimal PK and PD profile for elvitegravir.

These data present the concentration time profile of elvitegravir. The X axis is time, and the Y axis is elvitegravir plasma concentration.

This is elvitegravir in the unboosted state. Here, I'm showing you the IC50 and the IC95, both protein binding adjusted for elvitegravir. As you can see, in the unboosted state, the compound has a relatively short half-life, with concentrations that fall below the IC95 as well as close to the IC50 after 12 hours after administration. This would mean that we would need to administer high doses and twice daily doses to achieve coverage above the protein binding adjusted IC95.

In contrast, this is elvitegravir's concentration time profile in the boosted state with 100 milligrams of ritonavir. As you can see, there's a substantial increase in its plasma exposure, a much longer half-life, which opens the potential for once-daily dosing at low doses.

We wanted to understand this in great detail, and we conducted a clinical study in healthy subjects to understand the potential of boosting of the most commonly used compounds that's used for boosting, ritonavir, and how it related to elvitegravir exposures.

These data present the clearance of a validated CYP3A probe administered to healthy subjects at baseline on the left-hand portion of the figure and with a variety of doses of ritonavir, a booster, 20 milligrams, 50 milligrams, 100 and 200 milligrams. As you can see here, even low doses of ritonavir substantially inhibit CYP3A mediated metabolism. The 100-milligram dose, that dose that is most frequently for boosting, results in an 85 percent reduction in the clearance by CYP3A.

These data now show elvitegravir exposures when administered with these various doses of ritonavir, and at the 100 milligram dose of ritonavir, over a 20-fold increase in elvitegravir systemic exposures. This really established proof of concept for developing elvitegravir as a boosted drug.

In parallel with this study, we were conducting a monotherapy study of elvitegravir to understand its antiviral activity in HIV-infected patients. These are the results from this study.

In this study, we evaluated a variety of elvitegravir doses, both administered once a day and twice a day in the unboosted state as well as a once-daily dose in the boosted state. As you can see from this viral dynamic plot, elvitegravir demonstrated potent anti-HIV activity as monotherapy with a variety of doses, achieving a log reduction in HIV RNA of approximately 2 logs from baseline.

Importantly, since we varied the dosing regimens of elvitegravir as well as the doses, we can disconnect the various PK parameters to best understand which PK parameter for elvitegravir was most associated with advanced HIV activity. And those data are presented on the next slide.

Here, I'm sharing with you data from three of the cohorts. This 400 milligram twice-a-day cohort, you'll note that the max change in HIV RNA was approximately 2 log, and the trough concentration was over the protein binding adjusted IC95, approximately 50 nanograms per mL.

In contrast, an 800 milligram once-daily

dose – so the same total daily dose but administered once a day – which provided a higher Cmax in a similar area under the curve but a much lower trough, suffered a severe decrement in anti-HIV activity. This illustrates the trough concentration of elvitegravir is most associated and important as it relates to its anti-HIV activity.

Last, these data show a low 50-milligram dose of elvitegravir co-administered with 100 milligrams of ritonavir provides a high trough concentration and maximal anti-HIV activity. And this low dose amenable for co-formulation.

Following this monotherapy study, we moved forward for elvitegravir in treatment-experienced patients in a phase 2 study. Since these were treatment-experienced subjects, they received an optimized background regimen by genotyping, and they received one of three elvitegravir doses or a comparator protease inhibitor.

In this study, elvitegravir at 125-milligram dose outperformed the lower elvitegravir doses as

well as the comparator protease inhibitor. Importantly, the 125-milligram dose in this study provides equivalent exposure to the 150-milligram dose of elvitegravir that's contained within the QUAD. This difference in dose is due to changes in formulation and manufacturing as the program advanced.

So in terms of performing final dose selection for elvitegravir, we performed a number of analyses, including Emax modeling for antiviral activity. This plots elvitegravir trough concentration on the X axis on a logarithmic scale and changing HIV RNA on the Y axis.

Based on Emax modeling, we identified a maximal anti-HIV activity of over 2 logs from both our phase 1 and our phase 2 studies in HIV-infected patients. Importantly, this program evaluated over a 20-fold range in elvitegravir trough concentrations, and we identified that the exposures associated with the 150-milligram dose provided near maximal anti-HIV activity.

Also, by providing a mean trough tenfold

above the protein binding adjusted IC95 and understanding the PK variability of elvitegravir, we would expect that this dose would provide trough concentrations of EVG in all patients above the protein binding adjusted IC95. And based on this, we selected the 150-milligram dose.

So as we moved forward to bring elvitegravir into treatment-naive patients, we were faced with the challenge of how do we develop this drug that has optimal PK and PK in the boosted state with ritonavir even at a 100 milligrams, which has protease inhibitor activity, potentially. It could select for resistance. And how do you prove the negative that it can't select for protease inhibitor resistance?

It was because of this we decided to move forward with the development of cobicistat. Other challenges associated with using ritonavir as a booster, that it's difficult to co-formulate, it has some side effects, and there are some unwanted DNPK properties, specifically inhibition of some drug metabolizing enzymes as well as induction of

drug metabolizing enzymes in transporters.

The bottom portion of this slide presents really the key data that allowed cobicistat to move forward, and that was removal of anti-HIV activity. On this slide, you'll see that cobicistat relative to ritonavir does not have activity against the HIV-1 protease enzyme or in cell-based assays.

Once we removed anti-HIV activity, the next order of business was mimicking the CYP3A inhibition afforded by ritonavir, both the competitive but more importantly, the mechanism-based inhibition.

A mechanism-based inhibitor is unique in that its metabolism is what actually inactivates the CYP3A enzyme, preventing it from metabolizing any subsequent substrate. It requires re-synthesis of the enzyme as opposed to a competitive inhibitor which has to maintain a high concentration throughout the dosing interval. Ritonavir has this effect, and these data show that both cobicistat and ritonavir are potent and efficient mechanism-based inhibitors of CYP3A.

We also evaluated cobicistat's ability to inhibit other CYP enzymes relative to that of ritonavir. For some CYP enzymes such as CYP2C8 and 2C9 and for UGT1A1, which is a phase 2 metabolizing enzyme, cobicistat has less inhibitory potential in vitro relative to ritonavir. Both cobicistat and ritonavir are similar but weak inhibitors of CYP2B6 and CYP2D6.

Last and an important consideration in the development of cobicistat was to remove this unwanted or off-target effect of ritonavir induction. Induction of drug metabolizing enzymes or transporters is most often mediated via activation of human PXR, a nuclear factor.

The left-hand portion of this slide shows that relative to ritonavir, cobicistat does not activate human PXR. On the right-hand portion of this slide is the output of activation of PXR, messenger RNA of CYP3A. As you can see, a variety of cobicistat doses, including doses that are super therapeutic, do not induce messenger RNA of CYP3A relative to a positive control, in this case,

rifampin.

At this point, we moved forward and brought cobicistat into the clinic and wanted to perform the same detailed assessments of its PD, specifically, its anti-CYP3A activity, similar to what we did for ritonavir with elvitegravir. Again, we conducted a clinical study in which healthy subjects received the CYP3A probe, midazolam at baseline, as represented by the left bar. We used ritonavir 100 milligrams as a positive control. You see a 95 percent reduction in the clearance of this CYP3A substrate. And we looked at a variety of cobicistat doses, 50, 100 and 200 milligrams.

These data provided clinical proof of concept for cobicistat as a booster, and it also allowed us to zero in on a potential dose somewhere between 100 and 200 milligrams for boosting elvitegravir.

At this point, we moved forward with final dose selection of cobicistat directly within the context of the QUAD tablet. We manufactured a

variety of QUAD tablets where we varied the cobicistat dose.

Data from this study is presented here. I'm showing you data for 100-milligram dose of cobicistat, 150-milligram dose of cobicistat, and then the control in the study, elvitegravir boosted with 100 milligrams of ritonavir.

The 150-milligram dose of COBI provided our target trough concentrations of tenfold above the protein binding adjusted IC95, as shown by the IQ on this slide, of over 450 nanograms per mL. The 100-milligram dose of cobicistat was not able to achieve this profile. Based on this, we picked the 150-milligram dose of cobicistat in the QUAD.

It was about this time in the development program where we noticed in phase 1 studies in healthy subjects small changes in serum creatinine, increases in serum creatinine, and decreases in estimated GFR in patients that received either COBI or the QUAD. These data are presented here. Healthy subjects in phase 1 studies who received either COBI or QUAD experienced rapid and

approximately .1 to .2 milligram per deciliter increases in serum creatinine which translated into decreases in estimated GFR based on serum creatinine, specifically, Cockcroft and Gault equation derived measures. We did not see this effect in healthy subjects who received the nucleoside backbone Truvada.

When looking at these data in greater detail, we looked at a variety of different COBI doses, data from studies of different COBI doses as represented on the bottom Y axis in the orange bars, and the change in estimated GFR is represented on the top X axis in the gray bars.

In these analyses, we saw a dose dependent effect of cobicistat on decreasing estimated GFR. Also, the timing of these changes occurred almost immediately upon dosing within the first one to two doses, seemed to stabilize in these studies in a short period of time and then immediately returned to baseline upon cessation of study drug.

Based on these data, we suspected we may be observing a drug transport interaction, which has

been described for other compounds. We moved forward with the clinical study to assess this in detail.

Healthy subjects received either cobicistat, ritonavir, or placebo. We calculated their estimated GFR using the Cockcroft and Gault equation at baseline, on day 7 upon steady state administration of study drugs, and then on day 14 after a seven-day washout of study drugs.

In this study, we also administered a probe substrate, iohexol, which is a contrast agent that's filtered by the glomerulus, again, at baseline, on day 7 and on day 14.

These data, these are the results of the study. On the left-hand portion of the slide, you see eGFR by Cockcroft and Gault, and on the right-hand portion of the slide, you see actual GFR, the clearance of iohexol, the administered probe drug.

Consistent with our other phase 1 studies, we saw a change in estimated GFR on day 7 relative to day zero that returned to baseline on day 14. In contrast to estimated GFR, actual GFR was

unaffected on day 7 or day 14 relative to day zero. This lended additional evidence to the fact that cobicistat could affect serum creatinine, potentially via a drug transporter interaction.

Subsequent to this work, our preclinical colleagues have conducted a number of investigations in terms of the cationic transport pathway of creatinine and have identified that both cobicistat and ritonavir can inhibit the MATE 1 transporter that is responsible for the efflux of creatinine from the proximal tubule. Both cimetidine and trimethoprim, other compounds that are protypically known to increase serum creatinine, also have the potential to inhibit MATE 1.

I shared with you earlier that tenofovir disoproxil fumarate, the pro drug, is a substrate for p glycoprotein and that cobicistat as well as ritonavir can inhibit p glycoprotein and slightly increase the oral bioavailability of tenofovir.

These data show tenofovir PK in 419 HIV-infected patients that received the QUAD in the

phase 3 program. These data now show the concentrations of tenofovir in HIV-infected subjects as well as healthy subjects who have received tenofovir, either as tenofovir or Truvada, with ritonavir-boosted protease inhibitors, atazanavir, lopinivir/ritonavir or darunavir/ritonavir.

Data from the QUAD development program demonstrate the tenofovir levels in HIV-infected patients receiving the QUAD are similar to and not higher than tenofovir exposures that subjects who have received tenofovir since its approval in 2001 when they used it with a ritonavir-boosted protease inhibitor.

I'm now going to shift gears a little bit and walk you through some PK/PD analyses from our QUAD program confirming dose selection of elvitegravir and cobicistat.

This is the Emax dose response curve for elvitegravir from the elvitegravir early development program from phase 1 and phase 2 studies. These data now show elvitegravir PK/PD in

patients that received the QUAD from its phase 2 and phase 3 studies. You'll note that the EVG trough concentrations have met its target profile with a mean concentration of tenfold above the protein binding adjusted IC95, and all patients achieved this concentration above the protein binding adjusted IC95, supporting appropriate dose selections for both cobicistat and elvitegravir. We've also looked at this as it relates to the primary endpoint in the phase 3 studies that Dr. Szwarcberg will be walking you through.

These are the PK/PD results of elvitegravir trough concentrations by quartile of exposure as it relates to antiviral efficacy as assessed by the primary endpoint, the FDA snapshot algorithm.

Over the elvitegravir trough range from 54 nanograms per mil on the low end to over 2,000 nanograms per mil on the high end, we see high rates of virologic response consistent with being on the flat part of the dose response curve for elvitegravir boosted with cobicistat as the QUAD, confirming appropriate dose selection of both these

new chemical entities.

As it relates to drug-drug interactions, this is a boosted regimen, and so it will be subject to a number of important drug-drug interactions. Cobicistat is a potent CYP3A inhibitor, a weak 2D6 inhibitor, and a weak PGB inhibitor.

Elvitegravir is a modest CYP3A inducer, however, this is blocked in the setting of co-administration with cobicistat and a weak CYP2C subfamily inducer. Broadly speaking, administration of this boosted regimen will be consistent with the management of patients that receive other boosted ritonavir PI regimens.

Here are some examples. As you'd expect for a regimen that is a potent CYP3A inhibitor, there will be contraindications with narrow therapeutic index drugs metabolized via this pathway, most importantly, the orally administered sedative hypnotics and some of the statins.

For CYP2C due to potential for low level induction due to elvitegravir, we would recommend

monitoring compounds that are narrow therapeutic index and substrates for this metabolic pathway. And warfarin is a good example. In contrast to some ritonavir-boosted regimens, however, oral contraceptive use can be supported based on clinical data.

For CYP2D6 substrates, there may be modestly higher exposures due to inhibition by cobicistat, and we would recommend monitoring sensitive substrates metabolized via this pathway.

I shared with you the data I had for p glycoprotein as it relates to tenofovir exposures for narrow therapeutic index drugs that are PGB substrates. And digoxin being the validated probe substrate as well as the prototypical narrow therapeutic index drug that is monitored, you would want to monitor that closely.

And then lastly for hepatic uptake transporters that are more recently in the news and of interest, there could be slightly higher exposures. However, we conducted a clinical interaction study with rosuvastatin, which is a

substrate for all of these transporters and can provide clinical guidance regarding its use.

So in terms of product labeling, here is the QUAD as a victim of drug-drug interactions. As a boosted regimen, we were using cobicistat to provide high trough concentrations of elvitegravir. We do not recommend co-administration with potent inducers of CYP3A. And this is consistent with ritonavir-boosted PIs.

Additionally at this time, we would not recommend co-administration with other compounds that are known CYP3A inducers, again, in the interest of providing maximally effective elvitegravir trough concentrations in all patients.

So in summary of the QUAD early development program, we conducted comprehensive dose ranging and dose finding for both new chemical entities, elvitegravir and cobicistat. We've identified the trough concentrations or the key PK parameter associated with its anti-HIV activity, and that 150-milligram dose provides that maximal activity and high rates of suppression in patients, and that

the cobicistat dose of 150 milligrams maximally inhibits CYP3A and provides those target trough concentrations. And these have been validated through PK and PD analyses from our QUAD phase 2 and phase 3 program.

We've identified and characterized the COBI transporter interaction on serum creatinine. And in terms of drug-drug interactions, we've a plan for providing safe use that is consistent with management of ritonavir-boosted PI regimens.

Thank you, and I'll now turn over the sponsor's presentation to my colleague, Dr. Szwarcberg.

Sponsor Presentation – Javier Szwarcberg

DR. SZWARCBERG: Good morning. My name is Javier Szwarcberg. I work at Gilead conducting HIV clinical research.

QUAD is a novel once-daily integrase-based single tablet regimen that has a favorable efficacy, safety and tolerability profile for the treatment of adults with HIV infection. In addition to the phase 2 and 3 clinical studies that

we've conducted supporting the QUAD NDA, which was submitted in October 2011, Gilead has conducted additional studies in treatment-naive patients for the COBI tablet as well as treatment-experienced patients for the EVG tablet. Gilead plans to submit the NDAs for those two agents in the second quarter of 2012.

I will include in my presentation relevant COBI data as it informs QUAD safety.

Exposure to QUAD, COBI and EVG was large; 912 patients have been exposed to the QUAD tablets; 977 have been exposed to the COBI tablets, and 1,701 patients or subjects have been exposed to the EVG tablets. In total, including the COBI tablets, 1,889 patients have been exposed to the QUAD- or a COBI-containing regimen., and 2,613 have been exposed to a QUAD- or an EVG-containing regimen.

The duration of exposure in the phase 2 and 3 studies for the QUAD, included in the application, range between 48 weeks and 144 weeks. This large development program allows for a comprehensive characterization of QUAD's efficacy

and safety. The comparator's that we've chosen for the phase 2 and 3 studies are guidelines preferred regimens -- when I allude to guidelines, I mean the Department of Health and Human Services.

Both phase 3 studies were randomized, double-blind, double-dummy, active controlled and were stratified by baseline HIV RNA. Study 102 compared the QUAD relative to Atripla and was conducted solely in the U.S. Study 103 compared QUAD relative to a boosted PI plus Truvada and was an international study with 54 percent U.S. representation and 46 percent ex-U.S. representation and included countries from Europe, Australia, Thailand and Mexico. Both studies continued blinded through 192 weeks.

Entry criteria was identical for both trials. Both enrolled treatment-naive subjects that required to be sensitive to efavirenz, FTC and TDF in Study 102 and atazanavir, FTC and TDF in Study 103.

Screening GFR was set at greater than 70 at entry. This was to avoid early discontinuations

due to COBI's effect on creatinine secretion. Given that the QUAD tablet cannot be dose adjusted, the protocol required that patients that dropped their GFR while on treatment below 50 discontinue study drug. And this was to comply with the FTC and TDF labeling recommendations, which require dose adjustments when GFRs drop below 50.

The next slide presents the statistical analysis that we've used to analyze the primary endpoint. The primary endpoint assessed the proportion of patients that were on their original study treatment and were suppressed at week 48 using the FDA defined snapshot algorithm. Unlike earlier analysis such as time to loss of virologic response or TLOVR, which looked at achievement and maintenance of virologic suppression through the entire treatment period, snapshot looks at the response during the week 48 window.

Non-inferiority between the two treatments would be claimed if the lower bound of the confidence interval was greater than minus 12. And both studies were adequately powered at greater

than 95 percent.

Study 102 targeted to enroll a representative population of HIV-infected patients. Most patients were males in their late 30s. Roughly 40 percent of patients were non-whites, and about 30 percent of them were African American.

About a third of the patients had an HIV RNA of greater than 100,000, and the number of patients with a mean CD4 cell count was roughly in the high 300s. eGFR entry was around 115 for the QUAD group and 114 for the Atripla. This was measured by Cockcroft and Gault equation.

The study had high rates of completion. Approximately 350 patients enrolled into each of the treatment arms, QUAD and Atripla. Rates of discontinuations were low at 11 percent for the QUAD and 13 percent for Atripla, with 12 patients discontinuing due to adverse events in the QUAD group and 18 patients discontinuing due to adverse events in the Atripla group. The next most common reasons for discontinuation were lost to follow-up.

Study 102 met its primary endpoint with high

rates of virologic suppression of 88 and 84 percent for QUAD and Atripla. The lower bound of the confidence interval was minus 1.6, which is well within the required margin to determine non-inferiority, demonstrating a treatment effect that was at least comparable to Atripla. Of note is that the 84 percent response rate that one sees for Atripla is among the highest this combination has ever achieved in registrational trials.

The next slide shows different sensitivity analysis that we've conducted to compare the efficacy of the QUAD using different analyses. Other endpoints assessed include TLOVR using a ITT population, missing equals failure also for the ITT population and a snapshot looking at the protocol population and a missing equals excluded analysis. All show high response rates which are consistent with the primary analysis results.

Efficacy of subgroups also show a consistent treatment effect. This slide shows the efficacy of QUAD relative to Atripla by different subgroups of age, sex, race, baseline HIV RNA, baseline CD4 cell

count and a post-randomization variable of study drug adherence as measured by pill count.

In the forest plot, difference in the rate of virologic suppression between QUAD and Atripla for the different subgroups is plotted with a solid circle in a 95 percent confidence interval denoted as a bar. Most point estimates on the forest plot favor QUAD.

A closer look at the percent of patients suppressed looking at viral load and CD4 cell count is presented in this slide which reveals that even the generally more difficult to treat subgroups, those with HIV RNA and patients with CD4 cell counts less than 350, had comparable rates of virologic suppression between QUAD and Atripla. Both QUAD and Atripla also had high rates of virologic suppression looking at different subgroups of demographics of age, sex and race. This was looked at as well as in the prior slide, looking at the FDA snapshot algorithm.

Both QUAD and Atripla had similar rates of virologic success for all baseline demographic

subgroups of younger patients and older patients, males and females and whites versus non-whites.

In the next slide, I'll show the improvement in CD4 cell count, which is a marker of immunologic recovery. Both QUAD and Atripla had good responses. Changes in CD4 cell count at week 48 favor QUAD.

I will now discuss the second phase 3 trial, Study 103. Baseline characteristics were balanced between treatment groups. As I mentioned before, Study 103 was an international trial with 54 percent of subjects coming from the U.S. Most subjects enrolled were in their late 30s and were male. About a third of the patients were non-whites, and 20 percent were black or African descent. Roughly 40 percent of patients had an HIV RNA of greater than 100,000, and around 370 patients had -- the mean CD4 cell count was around 370. eGFR, like in Study 102, was around 113 for QUAD and 115 as measured by Cockcroft and Gault equation.

The next slide shows patient disposition

which show high rates of completion through week 48. Approximately 350 patients were enrolled into each of the treatment groups. The rate of discontinuations were low at 9 percent for the QUAD group and 11 percent for the atazanavir boosted by ritonavir plus Truvada.

Thirteen patients discontinued due to adverse events in the QUAD group, and 18 patients discontinued due to adverse events in the atazanavir group. The two most common reasons for discontinuation that follow adverse events were lost to follow-up and patient noncompliance.

Study 103 also met its primary endpoint. Virologic success rates were high for both QUAD and atazanavir at 90 and 87 percent with a lower bound of a confidence interval of minus 1.9, again, well within the required margin of minus 12. Like Atripla in Study 102, the virologic suppression rates that were observed for atazanavir in this trial were robust and among the highest reported with a boosted protease inhibitor.

Sensitivity analysis of virologic response

supports the primary endpoint. In addition to the primary, secondary and tertiary endpoints display high efficacy in each of the treatment groups, TLOVR, missing equals failure, snapshot per protocol, and missing equals excluded.

As with Study 102, analysis of subgroups in Study 103 show a consistent treatment effect. This slide shows the virologic response rates by subgroups of age, sex, race, baseline HIV RNA, baseline CD4 cell count, and study drug adherence as measured by pill count. Most point estimates favor QUAD.

A closer look at the virologic response rate for patients with HIV RNA subgroup and CD4 cell count is presented in this slide. As you can see, both QUAD and atazanavir had high rates of virologic suppression across the treatment subgroups.

Here we have the breakdown of efficacy by age, gender and race showing that across different baseline demographic subgroups in Study 103, response rates were high for both QUAD and

atazanavir.

Now, let's look at changes in CD4 cell count. High CD4 cell count improvement of above 200 cells were seen in both groups, and these results were consistent with the 102 findings.

Resistance analysis was conducted in all patients that failed and had more than 400 viral copies. The next slide shows the resistance analysis for Study 102, both of the phase 3 studies, Study 102 and Study 103. Study 102 is on your left, and Study 103 results are your right.

Greater resistance to any regimen component was low. Overall resistance to QUAD developed in under 2 percent of subjects in both studies combined. Resistance to the Truvada component was also low. And QUAD patients with EVG resistance also developed the MI84V/I mutation.

Resistance to EVG as part of the QUAD was 2 percent and 1.1 percent for Study 102 and Study 103. And resistance to efavirenz as part of Atripla was 2.3 percent. No subjects developed resistance to atazanavir as high barrier to

resistance is a known feature of protease inhibitors. Although a few patients in QUAD developed secondary protease inhibitor resistance, none had primary resistance.

In conclusion, with respect to efficacy, no inferiority was demonstrated for the primary endpoint of virologic suppression using the FDA snapshot algorithm in both studies with high rates of virologic suppression against guideline recommended first line regimen Atripla in atazanavir boosted by ritonavir plus Truvada.

Results were robust and consistent across treatment groups, specifically for baseline demographics and HIV characteristics, including patients with high viral load. Overall rates of resistance development were low at under 2 percent across studies. Collectively, these results demonstrate the robust efficacy of QUAD.

Let's now look at safety findings. Although I'll present safety data either integrated or by study, the key focus of the safety section is on integrated data from the phase 2 Study 104 and both

phase 3 studies, 102 and 103.

Let's begin with the extent of exposure to study drug. Close to 700 patients or 92 percent of the patients randomized to QUAD received study drug for 48 weeks, and approximately 350 patients received study drug for 72 weeks. This large number of patients exposed to QUAD in phase 2 and 3 studies forms the basis for the safety assessment.

This first slide shows the overall summary of adverse events. Most adverse events were mild to moderate with only 12 percent of patients having Grade 3 or 4 AEs in QUAD, 11 percent on Atripla, and 14 percent on atazanavir.

Also low were the rates of adverse events leading to study drug discontinuation, at 3 percent for QUAD, 5 percent for Atripla and for atazanavir. Only 9 percent of patients on QUAD had serious adverse events compared to 7 percent on Atripla and 9 percent on atazanavir. There was one death in the QUAD group, two deaths in the Atripla group, and three deaths in the atazanavir group. None of the deaths were considered related to study drug.

The next slide summarizes common adverse events in Study 102 and 103 separately. Similar to the threshold used by FDA in Table 6 in the briefing document, common AEs occurring in greater or equal than 3 percent of patients in QUAD with a difference of greater or equal to 3 percent between QUAD and either control group are summarized.

In Study 102, rates of diarrhea, nausea and headache were frequent for both QUAD and Atripla, but more common in QUAD. They were mostly mild to moderate, self-limited and rarely led to study drug discontinuation.

Certain neurologic and rash adverse events were higher in the Atripla group. This included abnormal dreams, insomnia, dizziness and rash. These tended to be longer lasting, and in some patients led to study drug discontinuation.

In Study 103, rates of diarrhea were lower in QUAD versus atazanavir, and rates of nausea and headaches were balanced between QUAD and atazanavir. Rates of abnormal dreams were lower in the QUAD group in Study 103 than in Study 102, and

it is explained by efavirenz's known safety profile as part of Atripla in Study 102.

The next slide shows serious adverse events in more than two patients in the QUAD group. The overall rate of serious adverse events was low at 9 percent for QUAD, 7 percent for Atripla, and 9 percent for atazanavir. SAEs reporting more than two patients in any treatment group included appendicitis, cellulitis and pneumonia. These three infections were infrequent at 0.7 percent, and all were unrelated to study drug.

Adverse events leading to study drug discontinuation in more than one patient in the QUAD group are reported on the next slide. Presented on the first row of the table are the overall rates of AIDS leading to study drug discontinuation, which was low at 3 percent for QUAD, 5 percent for Atripla, and 5 percent for atazanavir.

Events were generally balanced between groups. However, with respect to rash and renal events, 0.4 percent of QUAD patients experienced a

discontinuation due to rash relative to 1.3 percent on Atripla and 1 percent on atazanavir. 0.8 percent of patients discontinued study drug due to a renal event in the QUAD group relative to 0.3 percent in the atazanavir group. I will discuss the renal discontinuations in more detail later in my slide deck.

I'll discuss next the grade 3/4 general laboratory findings. Creatine kinase and GGT were slightly higher in Atripla than in QUAD due to atazanavir's inhibition of bilirubin metabolism. Grade 3/4 hyperbilirubinemia was more common or occurred in approximately 60 percent of patients in the atazanavir group.

The next few slides present individual study result data on lipids and bone mineral density. Let's start with lipids in Study 102. In this study, the use of QUAD resulted in lesser increases in total cholesterol and LDL cholesterol relative to Atripla, but higher HDL increases were seen with Atripla.

In Study 103, there were no differences in

any of the cholesterol parameters between QUAD and atazanavir. However, lesser increases in triglycerides are seen with the QUAD.

Tenofovir use has been associated with bone and renal effects. To address bone effects, we performed DEXA scans in a subset of patients in Study 103, which I'll present to you in the next slide. And to address renal effects, I'll present to you renal safety findings in slides that follow.

Both groups lost approximately 3 percent of bone mineral density at the spine and at the hip at week 48. This decline seems to stabilize at week 24 for the spine. We continue to follow these patients using DEXA scanning through 192 weeks to assess long-term bone safety. In an exploratory analysis looking at the proportion of patients with a change in BMD of greater than 3 percent, less patients on QUAD had a change in BMD that was greater than 3 percent for both spine and hip.

During the current study period, there were no differences in the rate of fractures at 0.8 percent for the QUAD and 1.7 percent for

atazanavir.

The next slide plots creatinine changes over time. As expected due to cobicistat's effect inhibiting creatinine secretion, there were greater median increases in the QUAD group. Displayed are median values with a corresponding intra-quartile range. The Y axis corresponds to the median change from baseline in serum creatinine.

At week 48, there were greater increases from baseline in serum creatinine for the QUAD group in yellow than for the Atripla group in light blue. The increase in the atazanavir group, by ritonavir group is in green and is comparable to the changes seen with QUAD. This decrease in the QUAD group occurred as early as week 2, tends to plateau at week 16 and remained stable through week 48.

Given the findings in the prior slide, grade 1 creatinine elevations were expected with QUAD due to COBI's inhibition of creatinine secretion. Comparable low rates of grade 2 and 3 creatinine elevations were seen across treatment

groups. Rates of hypophosphatemia were also low and comparable between treatment groups. Proteinuria at baseline was common in both studies at about 10 percent regardless of treatment arm.

This slide presents changes in graded urinary protein at the top of the slide and glucose at the bottom of the slide. Grade 1 proteinuria was common in all groups with high rates in QUAD. Grade 2 proteinuria was low in all groups, but more common in the QUAD group. On the bottom table are rates of graded glycosuria which were low and comparable between the treatment arms.

I'll present to you in the next slide a detailed analysis of QUAD renal safety. Since TDF and COBI are components of the QUAD and because TDF has been infrequently associated with renal impairment and COBI has an effect inhibiting creatinine secretion, we have performed a thorough analysis of renal safety in the phase 3 registrational trials with QUAD and COBI, which I'll present to you in the next slides.

In addition, in order to increase the sample

size of patients exposed to COBI and TDF for safety analysis, we've combined the patients from the COBI program with patients from the QUAD program. This effectively increases the sample size of COBI- and TDF-exposed patients to 1,143 patients.

I would like to describe to you the two studies from the COBI program included in this section. The phase 2 study, 105, and the phase 3 studies, 114, were randomized, double-blind, double-dummy, active control and allocated patients to atazanavir boosted by ritonavir plus Truvada relative to atazanavir boosted by COBI plus Truvada.

eGFR at entry for Study 105 was higher than 80 mils per minute, and the eGFR at entry for Study 114, which was the phase 3, needed to be greater than 70 mLs per minute. Week 60 data is included for Study 105, and week 48 data is included for Study 114.

I will first present in this section a description of the renal discontinuations in the QUAD and COBI studies. We'll then contrast how the

QUAD renal safety experience compares to prior studies that contain a TDF regimen. We'll then present the results of a thorough laboratory analysis that we've conducted in the QUAD dataset looking for previously unrecognized potential cases of proximal tubulopathy. And lastly, I'll discuss renal monitoring.

Discontinuations due to renal adverse events were infrequent. Out of 1,143 patients, 1.2 percent discontinued due to renal AEs from either QUAD or the atazanavir arm relative to 1 percent in the atazanavir boosted by ritonavir plus Truvada arm from Studies 103 as well as the arms from Study 105 and 114.

Out of this large database of 1,143 patients exposed to QUAD to atazanavir boosted by COBI plus Truvada, almost 99 percent of patients were able to continue study drug, or if they discontinued, they did it for a non-renal AE. Of the 14 patients that discontinued due to a renal AE, eight came from the QUAD program or QUAD studies, and six came from the atazanavir COBI plus Truvada.

I will discuss these 14 cases in detail, and we'll start with the eight QUAD patients first. Of the eight patients that discontinued QUAD due to renal AEs, the first four did it solely because of elevations in creatinine without evidence of proteinuria, glycosuria, or hypophosphatemia. Given that creatinine improved rapidly after QUAD was discontinued, we suspect that these elevations in creatinine were due to COBI's inhibition of creatinine secretion.

Next are the four patients on QUAD that experienced proximal tubulopathy with elevations in creatinine with glycosuria or proteinuria. Two of the four patients had GFRs at baseline that were below 70, but they qualified to enter the trial based on screening labs.

For them, QUAD was continued despite confirmed on treatment GFRs that were below 50, which constituted a protocol violation. In all four patients, renal function improved after QUAD was discontinued.

Next, I'll present the six patients that

discontinued due to a renal event in the atazanavir COBI arm from Studies 105 and Studies 114. Of the six patients that discontinued the ATV/co arm due to a renal AE, one discontinued due to elevations in creatinine without any evidence of proteinuria, glycosuria or hypophosphatemia. Creatinine improved rapidly after ATV/co plus Truvada was discontinued. And again, we attribute this elevation to COBI's inhibition of creatinine secretion.

The other five patients experienced tubulopathy with increases in creatinine along with proteinuria and glycosuria which improved after atazanavir COBI discontinuation in four patients. The fifth patient discontinued drug and from study after recovering from enterobacter sepsis with no follow-up data available.

I would like to summarize on the next slide the renal findings of the patients that discontinued due to a renal AE in the QUAD arms and the ATV/co arm.

Renal discontinuations were infrequent at

1.2 percent. Five renal discontinuations had increases in creatinine only, and those are likely attributable to COBI's inhibition of creatinine secretion. And nine renal discontinuations, which Gilead and the FDA agree on, experience proximal tubular dysfunction with creatinine elevations along with proteinuria and glycosuria.

Importantly, 13 out of the 14 cases improved upon QUAD or ATV/co plus Truvada discontinuation. And one patient discontinued due to enterobacter sepsis without available follow-up data.

So an important question that the FDA has asked Gilead to address is how does the renal safety experience in the QUAD program compare to other treatment regimens that contain tenofovir. The next few slides summarize key renal safety outcomes, including adverse events, graded creatinine and graded proteinuria with QUAD relative to TDF-containing large registrational studies and non-registrational studies with NNRTIs and ritonavir-boosted PIs.

The rates in the next few slides are the

same you saw yesterday during the PrEP meeting. Overall, rates of renal AEs, including renal discontinuations, serious renal adverse events and adverse events of proximal tubulopathy as reported by the investigators were low with QUAD. QUAD rates were slightly higher than with NNRTI regimens that are comparable to ritonavir-boosted PI.

The difference that we're observing between boosted and unboosted regimens, as remarked by Dr. Kearney in his presentation, is possibly related to tenofovir levels which tended to be 25 to 35 percent higher in boosted regimens.

With respect to changes in creatinine, you will notice that the sample sizes in this analysis is different than the one for the AEs in the prior slide. This is because some data was not published, and we were unable to get that data directly from the sponsors.

Most of the abnormal creatinine elevations were grade 1 at 6.4 percent with very few grade 2 and grade 3. This was expected due to COBI's inhibition of creatinine secretion, which leads to

creatinine increases.

QUAD rates were comparable to NNRTI base regimens, which upper range was driven primarily by rilpivirine studies and also comparable to ritonavir-boosted PIs. Rilpivirine and ritonavir like COBI inhibit creatinine secretion, causing similar increases in creatinine.

Proteinuria was common with QUAD with grade 1 at around 30 percent and grade 2 at around 6. These rates were higher to reported rates of proteinuria in studies containing NNRTI and ritonavir-boosted PIs.

I'll discuss next a comprehensive analysis of renal laboratory that we've conducted using the QUAD dataset looking for previously unrecognized potential cases of proximal tubulopathy. This analysis was conducted to determine whether there were any additional patients that developed underlying kidney disease, including proximal tubulopathy, while on QUAD but were not identified through standard investigator AE reporting.

To identify subclinical kidney disease, we

used the following criteria: a confirmed change in any of the following from baseline, creatinine greater or equal to 0.4 milligrams per deciliter increase, normal glycemic glycosuria greater to equal to one grade increase, hypophosphatemia greater or equal to one grade increase, and proteinuria at greater or equal to two grade increase which is our interpretation of a substantive increase as it was characterized in page 22 of the FDA briefing document.

Of the 749 patients exposed to QUAD, eight discontinued due to renal AEs and are not the focus of this analysis. And the remaining 741 patients, 17 had one laboratory abnormality. Of note, no patients had overlapping abnormalities, as I'll show you next.

Thirteen patients experienced creatinine increases that were greater or equal to 0.4. All 13 continued on study drug and did well. Their creatinine values either remained stable or improved over time. No patients developed at least a grade 1 increase in urinary glucose with

concurrent normal glycemia or abnormal glycemic glycosuria.

Three patients developed a confirmed one grade increase in hypophosphatemia. In all, serum phosphate fluctuated and generally returned to normal values while on study drug. And lastly, one patient who had proteinuria at baseline developed a confirmed two grade increase in proteinuria, but this finding occurred in isolation without glycosuria, hypophosphatemia or elevations in creatinine.

This comprehensive laboratory analysis demonstrates that no additional cases of subclinical kidney disease or of proximal tubulopathy were identified among QUAD patients.

As part of renal safety monitoring, several laboratory parameters were measured in the QUAD studies and available to investigators to dictate care. At every scheduled study visit, serum creatinine, serum phosphorous, urinary protein and urinary glucose were drawn.

Using the laboratory parameters above,

investigators identified four cases of proximal tubulopathy in QUAD studies. These four cases were the four cases that were in the QUAD program which Gilead and the FDA agrees.

Given that creatinine is widely available and convenient to use, we explored a cutoff to distinguish between COBI's inhibition of creatinine secretion and potential tenofovir toxicity.

Increases in creatinine are expected due to COBI's inhibitory effect on creatinine tubular secretion. Creatinine increases as large as the mean plus two times the standard deviation represent the change that is unlikely due to COBI. An increase in creatinine of greater or equal to 0.4 was present in all cases of proximal tubulopathy identified by Gilead and by FDA.

Based on the data presented, the next slide summarizes the proposed renal monitoring recommendations for patients on QUAD. eGFR is to be calculated and urine protein measured prior to therapy in all patients. This is to establish a baseline and to be able to interpret changes.

The QUAD should not be initiated in patients with eGFR of less than 70 mLs per minute. Confirmed increases in creatinine of greater or equal to 0.4 while on therapy require close monitoring, and changes that are lower or lesser than 0.4 are expected due to COBI. The patients should discontinue if eGFR drops below 50 mLs per minute, and concurrent use of nephrotoxic drugs should be avoided.

In conclusion with respect to safety, the QUAD was well tolerated with most AEs being mild to moderate and with low rates of discontinuation due to adverse events. QUAD had a favorable safety profile relative to Atripla and to atazanavir.

Relative to Atripla, there were less neurologic and rash adverse events and smaller increases in total cholesterol and LDL cholesterol. Relative to atazanavir, there are less bilirubin-related adverse events and less grade 3, 4 hyperbilirubinemia. Also, there was more increases in triglycerides.

The QUAD renal profile is consistent with

TDF when given along with a boosted PI. Renal events were monitorable, relying on creatinine with 1.1 percent of subjects discontinuing study drug due to renal AEs which improved or reversed upon discontinuation. Smaller increases in creatinine are expected due to COBI's inhibition of creatinine secretion, and this does not represent renal toxicity.

Dr. Cheng will now return to conclude the sponsor's presentation.

Sponsor Presentation – Andrew Cheng

DR. CHENG: QUAD has the potential to fulfill an unmet medical need for our patients with HIV infection. Some of the beneficial features include that it is a single tablet, once-daily, one pill, and it is the first once-daily integrase inhibitor. It is proposed to be a pregnancy category B drug and has activity against non-nucleoside resistant HIV. It is built upon the preferred nucleoside backbone represented by the DHHS guidelines.

As I touched on earlier, it is well

characterized with roughly 9 million patient years of tenofovir exposure and 4 million patient years of FTC exposure.

The development program has revealed many important benefits of QUAD. In terms of efficacy, it has a 88 to 90 percent of virologic suppression, among the highest seen in registrational studies. It is non-inferior to Department of Health and Human Services' preferred regimens of Atripla and atazanavir boosted by ritonavir.

The rate of resistance development is low by approximately less than 2 percent, and the regimen is well tolerated. Most adverse events were mild to moderate with less CNS and rash adverse events compared to efavirenz and less hyperbilirubinemia compared to boosted atazanavir.

Overall, the rates of adverse events leading to discontinuation are low. However, the QUAD does not come without risks. The renal events are the most predictable effects due to the increase in the serum creatinine levels due to cobicistat, which I want to remind you decreases estimated glomerular

filtration rates but does not address actual glomerular filtration rates.

The renal events that you've seen, proximal tubulopathy and the rates of adverse events, are consistent with a boosted PI and tenofovir. It is monitorable using serum creatinine, and it has expected cytokine 3A drug-drug interactions as it is a boosted compound.

However, these risks are predictable and monitorable. Taken together, they lead us to conclude that the benefit/risk profile of QUAD is positive due to the rates of virologic suppression, which are high; non-inferiority due to the preferred regimens, the low rates of resistance development and the overall well-tolerated nature demonstrated in the phase 3 studies.

The renal safety is comparable to tenofovir when given with a boosted PI. And lastly, it is another once-daily single tablet regimen.

Thank you very much.

Clarifying Questions from the Committee

DR. MURATA: Now that the sponsor's

presentation is concluded, we'll move on to clarifying questions. Again, I am reminded to mention the committee members to state your name before you speak. Also, this time period is intended for clarifying questions primarily for factual matters.

Dr. Ellenberg.

DR. ELLENBERG: I'd like to understand a little more about the designs of these two primary studies. First, can you explain the basis for the 12 percent non-inferiority margin, where that came from?

Secondly, I guess I'm a little confused. These are ongoing studies, and we're getting data based on some kind of a snapshot. And I'd like to understand what data might actually be available that we're not seeing. Is the safety data also cut off at 48 weeks? Do you have some kind of a consort figure that you can show who's in this and who's not and what additional data actually might be there that we are not seeing now?

So those two.

DR. CHENG: Thank you for your questions. It is a multiple part question, so perhaps I can start with the easier parts first, which is that the data you're seeing today is the 48-week primary endpoint. It is an ongoing 192-week study, so there are additional data that are available. We provided additional data from the safety database, in the safety update, that was a cut through the end of December of last year.

So those are the data that we have provided for this analysis.

Now, in terms of the non-inferiority margin, how was 12 percent chosen, I'd actually like Dr. Wolfson to come to the podium to address that.

DR. WOLFSON: I'm Michael Wolfson. I'm vice president of biometrics at Gilead Sciences.

So the 12 percent margin that was used for both pivotal trials was selected on the basis that it's the most commonly used threshold for non-inferiority for HIV-naive clinical trials.

Normally when selecting a margin, the actual delta that's used should be based on the

contribution of the active comparator. Truvada alone would never be ethical to be used as a intervention for HIV. So the actual magnitude of what efavirenz and atazanavir is contributing is actually unknown.

So in 2008, Hill compiled the studies that had been used in HIV, and of the 18 studies that he summarized, 14 used a margin of 12 percent. And so that was the basis of our selecting the 12 percent. Note that the actual observed lower bounds were very close to zero. They were minus 1.6 and minus 1.9.

DR. ELLENBERG: So basically, it's just kind of made up?

DR. WILSON: Correct.

(Laughter.)

DR. MURATA: Dr. Hunsicker.

Dr. Murray, sorry.

DR. MURRAY: Yeah, no, it's not made up. It's in our guidance for developing HIV drugs, and basically, Truvada or two nucs alone would give you zero, maybe 1 or 2 percent undetectable at 48

weeks. So adding the third drug, its contribution, in effect, in kind of this synergistic HAART regimen is maybe 80 percent.

So you have such a huge contribution that your M1, knowing that something that you want to know, that the third drug is contributing something, is so large, you could drive a truck through. So really, the 12 percent is an M2, and we could quibble over 12 percent is something you'd want to give up in treatment-naive.

But, in fact, when we power for 10 to 12 percent, you get non-inferiority margins usually, a couple cases not, that are very, very close, usually 3 percent, even closer, I think, for this case range.

So I think that we do know the contribution of atazanavir and ritonavir and efavirenz for many trials and from extrapolation, and it's huge. It's enormous.

DR. ELLENBERG: Right. So basically, if this is like sort of in vaccine trials when you expect it 80 to 90 percent effective, you have

highly effective regimens, and so the 12 percent is basically what you feel -- it's subjective, but it's what you feel you can give up. It's not really based on making sure there's actually still some effect like it is in many other -- is that right?

DR. MURRAY: Right, right. If it was 20 percent, even 40 percent, the non-inferiority margin, we would know that it was contributing something better than placebo.

DR. ELLENBERG: Thank you.

DR. MURATA: Dr. Hunsicker.

DR. HUNSICKER: I actually do have another question. Being one of the two nephrologists here, let me address the kidney question.

I see there are three issues, two of them, it seems to me are resolvable. The first is the elevation due to the COBI, which, to my mind, is a non-issue. The second is, well, you have to give the stuff with Truvada, and Truvada is associated with toxicity. But I think you're stuck with Truvada no matter what you do, and so I'm not sure

that that's an issue, although we have to discuss as a group what needs to be looked at in terms of long-term toxicity.

The third is the issue, is there, in fact, an interaction between COBI or the one that starts with E and the Truvada combination. And I'm getting sort of mixed signals. One of the things is that the levels of tenofovir are about 20 percent higher in the patients who are on COBI as opposed to the others, and the other is that there wasn't much difference in the drug levels.

I grant you that the numbers of adverse events is very small, but I think I'm still a little unsure whether there is either a pharmacokinetic or a pharmacodynamic interaction between these components. And I'd like to have you clarify that as best you can.

DR. CHENG: Thank you very much. I'd like to ask Dr. Kearney to come to clarify one of the points that you raised, which is whether or not there's a difference in the drug levels. You raised whether there's a 20 percent effect versus

almost no effect. I'd like him to speak to that, please.

DR. KEARNEY: So through its development program, tenofovir and then its clinical use in a number of drug interaction studies conducted by both us and other sponsors, we do see a reproducible effect of tenofovir exposure as being higher with boosted PI regimens.

May I have slide CC-40 up, please? There is variability from study to study, and cross-study comparisons are always challenging, but tenofovir levels are a bit higher in any boosted state relative to an unboosted state, I guess for the easiest way to state it.

QUAD is in the boosted state, as are these boosted regimens, and that increase is about 25 to 35 percent relative if you were to give tenofovir with these non-boosted regimens.

DR. MURATA: Dr. Strader.

DR. STRADER: I have a couple of questions. First, how many patients had diabetes and/or hypertension in the group? Do you have any idea?

DR. CHENG: I'll ask Dr. Szwarcberg to answer that.

DR. SZWARCBERG: There were roughly about 124 patients with hypertension and about 24 patients with diabetes enrolled in the QUAD program.

DR. STRADER: And did any of those patients have baseline elevations in creatinine entry into the studies that you're aware of?

DR. SZWARCBERG: I'll be happy to show you -- well, we did not exclude patients based on the urine analysis of patients with abnormal urine analysis, meaning urinary protein or urinary glucose were allowed into the trial. And, of course, some of the patients with diabetes had glycosuria.

DR. STRADER: Okay.

DR. SZWARCBERG: And some had proteinuria. But as we tracked those patients forward after they received study drug, their creatinine plots looked identical, almost identical, to patients that didn't have diabetes or hypertension.

DR. STRADER: Okay. On slide 69, where there is a difference between males and females who were treated, is that difference statistically significant, the 90 to 87 versus 83, 82? Was there a statistically significant difference between the response in males and females?

DR. SZWARCBERG: No, there's not.

DR. STRADER: No? Okay. Two more brief questions. One, you mentioned that the patients' creatinine or renal function improved. Do you have any actual numbers? What was the decreasing creatinine clearance? Did it return to normal, or was it just a mild improvement? Define improved.

DR. CHENG: Yes, so improved for the patients -- so there are two groups of patients. So the patients that only had a serum creatinine rise without any components of tubulopathy, once they discontinued, they returned to baseline. It was relatively rapid, not unlike what Dr. Kearney showed in the phase 1 HIV-negative study where people once after day 7 with cobicistat alone, they discontinued, and they sort of returned to normal

in serum and their estimated GFR.

With the other patients with tubulopathy, the tubulopathy returned pretty rapidly. The serum creatinine in some cases returned more rapidly; some cases more slowly. It was complicated by sometimes the other patients would go on to regimens that included drugs that boost serum creatinine levels such as rilpivirine, as Dr. Kearney showed on the previous slide, also inhibits tubular secretion of creatinine so it leads to a bump, or they went on to ritonavir-boosted protease inhibitor, which we showed in Study 103 also leads to a rise in serum creatinine. So that made the assessment of that component more complex.

DR. STRADER: Okay. And the final question is about the drug-drug interactions. You mentioned some drugs that are contraindicated. Are all strong inducers of CYP3A4 contraindicated? Did you do studies on things like nafcillin and Z efavirenz, Tegretol, carbamazepine, that kind of thing?

DR. CHENG: I'll ask Dr. Kearney to speak to that, please.

DR. KEARNEY: Like ritonavir-boosted PIs, strong CYP3A inducers are contraindicated. We also have some recommendations on there for moderate inducers to not be recommended, but they're not to the level of a contraindication.

DR. STRADER: Okay. So strong inducers, yes; moderate, no, but there are some recommendations on modification of dosing?

DR. KEARNEY: We do not recommend co-administration of moderate inducers, but it is not a contraindication --

DR. STRADER: I see. Okay. Thank you.

DR. MURATA: Dr. Giordano.

DR. GIORDANO: Thank you. I guess I have three questions. On slide CC-71, you showed the development of resistance across the entire study populations, as I read those data, and I wonder what the proportion of patients who had virologic failure who developed resistance was.

DR. CHENG: So I'd like to ask Dr. White to

come speak to that, please.

DR. MURATA: Please state your name.

DR. WHITE: Kirsten White, Gilead Sciences.

We do have a slide with the additional numbers that you request.

Slide up. Here we have the -- on the grayed out second row, the percentage of resistance development over the entire population. This is the integrated studies of QUAD as 1.7 percent.

When we determined the percentage of patients that were included in the resistance analysis population, it's 48 percent for QUAD, and this is similar to the 44 percent for Atripla.

DR. GIORDANO: Could you leave that up a minute more? So 38 percent developed resistance to the elvitegravir component similar to the 39 percent who developed resistance to efavirenz, and 44 percent developed resistance to the nucleoside, nucleotide backbone, which is higher than developed resistance in the efavirenz comparator. Okay. Thank you.

Second question is, for clarification, you

said a creatinine greater than .4 seemed to indicate -- in your proposed algorithm for monitoring safety, slide 116, if there was an increase greater than .4, that suggested this may be more than just inhibition of creatinine secretion.

It seemed to me that the way you arrived at that conclusion was a little circular because you only looked at patients who had a creatinine greater than .4. Am I mistaken on that? If their creatinine was less .4, you didn't seek them out in your analysis of renal adverse events.

DR. CHENG: Perhaps I could clarify that. So the creatinine .4 stems from what we observed as the standard deviation of the -- slide up, pleas.

So increase of .4 is really -- we saw 0.14 as the mean change in serum creatinine elevation for all patients, and then we looked at the standard deviation times two. And that's who we came up with the .4.

The other monitoring that we talked about on slide 120, that's sort of in a separate parameter.

This really is designed to distinguish between what is purely a cobicistat inhibition of serum creatinine compared to something else that we'd use for monitoring.

Once we had this as what the event is, we wanted to see if that was the case and we used that, how would that identify cases in order to try to validate, drive at your question.

DR. GIORDANO: So what proportion of the patients who had an increase greater than .4 and what proportion of the patients who had an increase less than .4 had some other indication of tubular damage, like increase in proteinuria or some glycosuria?

DR. CHENG: So when we look at .4, the false positive essentially what you're asking of the .4 is that there are 13 patients, roughly 2 percent of patients that had a 0.4 increase that did not develop any tubulopathy. The original patients on the -- that did discontinue are up on slide 8, are in the right-hand box up on the slide that looks at those that discontinued. Those that did not

discontinue, we have 13 patients, so roughly 2 percent of the group.

DR. GIORDANO: So those 13 patients, none of them had glycosuria, hypophosphatemia or proteinuria; is that --

DR. CHENG: Correct.

DR. GIORDANO: Okay. Now, of the 724 patients who had no abnormalities, which is defined as no increase in creatinine of at least .4, right?

DR. CHENG: Yes.

DR. GIORDANO: Did any of them have abnormal glycemic glycosuria, hypophosphatemia or proteinuria?

DR. CHENG: No.

DR. GIORDANO: Zero?

DR. CHENG: No. That's it.

DR. GIORDANO: Okay. Thanks.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: I have a couple of questions. One is for Dr. Kearney. You had shown on slide 37 the seven-day effect of exposure to COBI, which you'd explained was related to effects on tubular

transporter, but you'd also mentioned that you had done some studies with ritonavir, which has the same possible mechanism in terms of effect on the tubular transporter. And I was wondering if you could show the data on the ritonavir profile as well.

DR. KEARNEY: Sure. That slide's coming up. Let me speak to the results of that aspect of this study, which I didn't present for the sake of time.

We saw some of these changes in ritonavir patients in some of our early studies, and so we looked at the ritonavir as well. Ritonavir appears to have either a smaller effect or an effect that occurs maybe over a more prolonged period of time which you see in the Study 103 of the serum creatinine. It tends to go up a bit slower.

If I can have CP-134 here, this will show the results of the study here. This is serum creatinine that was measured every day in the study in the different groups that were studied in the study. So the black line with the gray dots is the placebo group, ritonavir is the purple bar, and

COBI is the orange bar. We had a subsequent cohort in this study where we wanted to look at effects in mild to moderate impairment. These people have a higher baseline serum creatinine, and they're reflected on this slide as well.

So in this study, we saw smaller effects of ritonavir than COBI on eGFR.

DR. ESTRELLA: Thank you. And then I guess I'm still a bit unclear in terms of what creatinine improvement actually was in the individuals who had a rise in their serum creatinine, specifically the four patients who were mentioned on slide 95 and sort of around that area.

I just wanted to know what the proportion was of the four that actually returned to baseline.

DR. CHENG: Okay. I'll ask Dr. Szwarcberg to speak to that.

DR. SZWARCBERG: I'd be happy to discuss with you the four cases in the QUAD group that discontinued due to a renal -- due to tubulopathy.

Can I have slide SA-90 up, please?

So this first patient discontinued fairly

early on around week number 4. This patient at week 2 had very high tenofovir levels or about 18,000, which was about fourfold the mean seen in the study. This was a 60-year-old white male who with baseline eGFR of 68. His entry eGFR into the study was around 70, so he qualified for entry into the study. And he has a history of hypertension.

Upon discontinuation of study drug at week 4, his creatinine trended down rapidly, and you can see that the patient was initiated between week 24 and 48 with a boosted PI and raltegravir. So maybe that's why you see sort of a ladder bump in the creatinine well after -- a long period of time after the patient had discontinued study drug.

With respect to proteinuria and glycosuria, they all returned down to normal upon study drug discontinuation.

The next patient also discontinued study drug rapidly. This patient was a 56-year-old white male with screening GFR of 67. The patient rescreened in the study and qualified for entry, and also had a past medical history of

hypertension.

Upon discontinuation of study drug, creatinine rapidly went down, and the patient was given a boosted PI, which explains the persistence of the creatinine over time. Proteinuria and glycosuria resolved after study drug discontinuation.

Can I have slide SA-92 up, please? This patient was a 20-year-old white male with eGFR at entry of 82, so below 90 percent, and trace urinary protein. The patient had a very slow increases in creatinine over time which peak at week 60, the time at which he was discontinued. He also had proteinuria and glycosuria, and proteinuria and glycosuria resolved and went back to normal values soon after study drug was discontinued. And creatinine dropped then -- I think is a little higher than how he was at baseline, but he was given rilpivirine, which is also a known agent which is known to inhibit the OCT2 transporter.

Lastly, the fourth case is a 29-year-old white male with proteinuria at baseline. He had

one plus. He was also given acyclovir during the study, which could confound some of what we're seeing here. But the patient had elevations in creatinine with glycosuria and proteinuria.

The glycosuria responded very well to study drug discontinuation. It went down to close to negative values. The last assessment was trace. This patient discontinued from study soon after discontinuation from study drug, so we have no further assessments, but you can see that the creatinine was trending down and at least the glucose component of a tubular marker resolved.

DR. ESTRELLA: One last quick question. For the patients who had isolated mild creatinine elevations, what was considered mild in those patients or those participants?

DR. CHENG: I'm sorry. Could you clarify your question?

DR. ESTRELLA: So on slide 94, there is a mention of four patients who had isolated mild creatinine elevations, and I just wanted mild to be defined for clarification.

DR. SZWARCBERG: The definition for mild was based on our graded definition for graded creatinine, and it was above 1.5. So it really changed, but it was due to the COBI effect.

DR. MURATA: Dr. Wood.

DR. WOOD: Thank you. My first question relates to the comment about the fact that COBI affects the estimated GFR but not the actual GFR. So the study was done that was presented on CC-37 was in 12 HIV-negative volunteers; is that correct? These individuals are HIV negative?

DR. CHENG: Yes.

DR. WOOD: So do you have any studies that have looked at eGFR as well as actual GFR in patients who are actually HIV infected to determine that indeed in patients with HIV infection who received the COBI that there is no change in eGFR versus actual GFR since HIV itself can be associated with nephropathy?

DR. CHENG: We do not have data at this time, although we have a study that will soon start.

DR. WOOD: Okay. Thank you for that clarification.

DR. HUNSICKER: I think that you do have some data that are relevant because I recall reading about cystatin GFR measurements, and the cystatin GFR measurement is creatinine independent. I think it was done in your HIV patients.

DR. CHENG: That is correct. However, we did not have iohexol in HIV-infected patients, but that's correct to assess that --

DR. HUNSICKER: Well, you might want to show that to Dr. Wood.

DR. CHENG: Sure. SA-49, please. So these are -- in Studies 102 and 103, we measured -- let me say cystatin C clearance, which is not secreted. It's a freely filtered moiety. It is affected by inflammation, though, as a marker. And you can see that over time that the increase between the QUAD arms and the atazanavir arms are roughly parallel.

DR. WOOD: Okay. All right. Thank you.

My next question is related to -- I tried to do it by slide numbers -- Excuse me -- C-99. The

question I had is the renal discontinuation.

Could you tell me what's the duration of exposure at the time of discontinuation? I don't really have a sense of is this early or late when people are discontinuing drugs in terms of related to the renal AEs. Do you have data that lets us know whether this is something early or is happening after several weeks or months?

DR. CHENG: So in the four cases that Dr. Szwarcberg just presented, two of them were relatively early within the first month, and two of them were later that occurred over time. That's more consistent with what we see with tenofovir in the long-term, slower rise, longer time.

DR. WOOD: Okay. And then for this group, did the same thing apply in terms of for these individuals that were described as related to renal discontinuations, was it kind of like some early, some late out of the 14?

DR. CHENG: Yes, yes, because these patients were out of the 105 and 114 studies, so the other patients were mostly on the later side.

DR. WOOD: Okay. Thank you. C-111, you explained that the four individuals -- oh, I wanted to know about for this group of individuals, were there any race or gender differences in terms of the individuals, the 17 patients who had these lab abnormalities? Did you see any race or gender differences in the individuals who were falling into these categories?

DR. CHENG: I'll ask Dr. Szwarcberg to come speak to that.

DR. WOOD: Okay.

DR. SZWARCBERG: We've not looked at individual gender differences for the 17 subjects that had isolated abnormalities and did not have evidence of subclinical kidney disease. But we've looked at demographic characteristics of the nine patients that discontinued study drug due to tubulopathy.

Can I please have slide SA-28 up? So out of the nine patients, the mean age was 43. Three patients were over 50 years old. Seven of them were male, which reflects the overall study

enrollment. CD4 cell count mean at baseline was 341. eGFR was below 70 in two patients, and an additional three patients had an eGFR below 90. Hypertension was present in two, diabetes in one, hepatitis C in one. And only one patient had screening proteinuria. No patients had proteinuria at baseline, and none of them had glycosuria at baseline.

DR. WOOD: Okay. And so presumably, four of these individuals are the white males that you talked about in detail earlier, and then the ethnicity of the remaining five?

DR. SZWARCBERG: So these are distributions of the seven. The other two were females. So seven -- so the four patients that I presented are part of a nine that I'm presenting in this slide. Four I've shown, which were male. There were another three that were males and two that were females so --

DR. WOOD: The race of those males?

DR. SZWARCBERG: Correct.

DR. WOOD: The race of the three remaining

males was white?

DR. SZWARCBERG: I'll have to look at that. I'll confirm to that, if I may, after lunch.

DR. WOOD: Sure, no problem.

DR. SZWARCBERG: Thank you.

DR. WOOD: Okay. Thank you.

The next question -- and it's just a general comment -- four females in CC-59 and CC-67, the confidence intervals are just much broader for females in terms of the percent difference in response by subgroup. And it was apparent in the 102 study and also in the 103 study.

And so are there any comments at all about this? It's just very interesting that it seems to be so much broader for females, and so do you-all have any explanation as it relates to either pharmacokinetics, pharmacodynamics, anything that kind of might explain why it's so broad? I was just struck by both of the slides, that it's so broad for females.

DR. CHENG: The reason is that this study had about 10 percent women between the two studies,

and it was disappointing to us.

DR. WOOD: All right. Just small statistical size?

DR. CHENG: Correct.

DR. WOOD: I'm almost done.

Then the other question I had, it was general, is do you have any sense that the discontinuations that you have or the observed changes that you see in creatinine, is there any relationship between certain pharmacokinetic parameters of cobicistat, either the trough levels, the Cmax, the AUC? Is there any relationship between pharmacokinetic parameters and then the renal parameters that we're monitoring that you guys observed?

DR. CHENG: Not in the discontinuations. I would note that, as Dr. Szwarcberg shared with you earlier, one of the four patients that did discontinue had a very high tenofovir levels. But not all the patients were in -- that patient happened to be in a PK sub-study, an intensive PK sub-study, and not all the patients were in the

sub-study. So it's not that they didn't have it. We just don't know.

DR. WOOD: So can you go back and look at those patients? Do you have bank specimens so that you might be able to back and specifically examine additional PK issues in those patients even --

DR. CHENG: I'll ask Dr. Kearney to speak to that.

DR. KEARNEY: So as it relates to Dr. Cheng's comment about tenofovir levels, expanding on that, it's kind of a chicken-and-egg situation where you have tenofovir that's eliminated by the kidney. And so if you have a situation of changing or declining renal function, it's hard to say whether it's a cause or effect.

We tried to understand that a little bit, including in the patients that participated in the PK sub-study, but it confounds the analysis. And as Dr. Szwarcberg said, in one of those patients, the person had -- it's the highest tenofovir level I've ever seen. We explored it to -- we were wondering if the person was taking more than one

pill or was taking other drugs, and we surveilled that patient but couldn't see it.

In terms of some of those other patients, those two clearly had higher tenofovir levels. The other two, they have some data points. They look like the regular population, population-based PK analyses. Once they moved towards having their event, though, their levels are a bit higher, as you would expect, as tenofovir is eliminated.

In terms of elvitegravir and cobicistat, we've done some analysis to look at whether exposures of those drugs are related to creatinine changes, and they're not.

DR. WOOD: Okay. The final question is to the sponsor as well as to the nephrology experts on the panel, and that is, are there any kind of pharmacogenomic markers that indicate susceptibility to proximal tubulopathy?

I don't know about this. I'm not eyeball deep in nephrology, but I was just wondering whether or not from a drug development standpoint if it's known that there are pharmacogenomic or

genetic markers that would identify individuals predisposed to having tubulopathy issues.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: So there have been a couple of studies looking at genetic variance that encode for the genes that encode for the transporters related to tenofovir, proximal tubular handling. So the organic and ion transporter in the MRP transporter, and there has been one reported for ABCC2, if I'm recalling correctly. But it hasn't been well validated and is not currently used clinically.

DR. WOOD: Thank you.

DR. MURATA: Dr. Hunsicker.

DR. HUNSICKER: If I could add just sort of in a generic sense, there are a whole family of things that can cause tubulopathies, and one assumes that there must be variance of the genes that cause overt disease that cause susceptibility. This is not well known, but clearly, there are going to be genomic differences between the people who do and don't. And we just don't know what they

are yet.

DR. MURATA: Okay. Let me proceed with the clarification questions here.

Dr. Daskalakis.

DR. DASKALAKIS: I'm so loud I always forget I need a mic. So I just wanted to ask about something that was covered in the FDA brief that was discussed briefly here but didn't go into a lot of detail. And that was there was an imbalance in secondary PI mutations on the cobicistat arm compared to non-cobicistat arms. And I know there's secondary not primary, but can we see some more about that?

DR. CHENG: Yes. I'd like Dr. White to come and address that, please.

DR. WHITE: So we have conducted a thorough analysis of any emergent resistance that occurred at the protease gene. The first analysis we did was the standard one to look for the emergence of primary protease resistance mutations, and we do this as part of our standard analysis. QUAD does not contain an active protease inhibitor.

So that we're all on the same page, the definition of a primary or major resistance mutation are that they're selected in vitro and in vivo by an active inhibitor and they confer reduced susceptibility to the drug on their own.

So on the diagram are the cumulative list of the known primary protease resistance mutations for the nine approved proteases, and we looked for the emergence of any of these. In the QUAD virologic failures, we found no patients with any primary drug resistance mutations to protease. These also had no phenotypic reduced susceptibility to any protease, and this includes no genotypic or phenotypic ritonavir resistance.

On the next slide, I'd like to show you those phenotypes. So here are the 27 patients in the QUAD group in our virology analysis population, and their phenotypic susceptibilities at failure to the nine approved protease inhibitors. The cells are colored green if they're called fully susceptible, and they would be red if there were any for reduced susceptibility.

So these data showed us that all QUAD virologic failures remained fully susceptible to all of their protease inhibitors.

We also looked at the emergence of any protease substitutions. So these would include secondary substitutions which can be polymorphic and only cause reduced susceptibility in the presence of a primary resistance mutation or any random substitution that may have occurred.

So looking specifically in the 102 QUAD versus Atripla, we found eight total substitutions that emerged in the protease gene out of seven subjects who had an emergent mutation in the QUAD group. And this was slightly higher than the four substitutions that occurred in the Atripla group out of the two patients that had an emergent resistance mutation.

However, this apparent increase was not confirmed when we look at the QUAD arm of Study 103 where we found five substitutions in two patients.

So our summary of the protease substitutions are that no patients on QUAD had emergent primary

resistance mutations. We have -- I can show you more detail on those other mutations, if you'd like, but our conclusions are that there was no clear signal of QUAD selecting substitutions in protease. And the data that support that conclusion are that these were naturally occurring at baseline in many patients. They were both gained and lost in the QUAD group, and many of them also occurred in the Atripla arm.

But we will continue to monitor for emergent resistance in the protease gene in our ongoing studies of QUAD.

DR. DASKALAKIS: Thank you very much.

Another question is, is the boosting dose of the COBI used in the atazanavir study the same as that in the QUAD?

DR. CHENG: Yes, it's 150 milligrams of cobicistat.

DR. DASKALAKIS: And in terms of drug-drug interaction studies, have you looked at how QUAD interacts with an unboosted PI because I would imagine that that will lead to -- there will

probably be co-administration if that's favorable.

DR. CHENG: Yes, we've conducted drug-drug interaction studies with 150 milligrams of cobicistat with atazanavir as well as with darunavir.

DR. DASKALAKIS: And then my last question just because there's a community concern about body morphological changes that occur with ritonavir, any biometrics looking at COBI, any sort of body morphological changes that have been identified? I know they're very short studies so it's hard to say, but any work done on that so far?

DR. CHENG: We have not identified any changes.

DR. DASKALAKIS: Thank you.

DR. MURATA: Mr. Raymond.

MR. RAYMOND: Thank you. A question about the enrollment criteria in the screening because it's striking that not only that there's the very low percentage of women in the study but also about only 3 to 5 percent with hepatitis C co-infection.

I'm just wondering whether this was a

function of the GFR cut point or some other screening criteria that disproportionately excluded these populations, or if it was more about study sites.

DR. CHENG: When we look at the entry criteria in terms of hepatitis C, U.S. spots specifically, I think it's important to remember these studies were enrolling in 2010. And one of the entry criteria was hepatitis C patients who did not intend to have hepatitis C therapy during the study. So we wanted to have co-infected patients, but if they were going to -- because of drug-drug interactions, if they were going to initiate other therapies, we encouraged them not to come into the study, especially in light of where the hepatitis C protease inhibitor drug development was at that time. So I think in that light, that may have lowered the number of hepatitis C patients that may have wanted to come on to the clinical trial.

DR. MURATA: Dr. Robinson.

DR. ROBINSON: Yes, several questions on the virology pharmacodynamic side. First, in your

resistance testing for the 184 and related, was this population sequencing that was done?

DR. CHENG: Yes, it was.

DR. ROBINSON: And was there any allele specific probing for low frequency resistance in the failure patients?

DR. CHENG: I'll ask Dr. White to come speak to that issue.

DR. WHITE: At this time, we did do population sequencing. We're currently in the process of doing clonal sequencing to look at linkage of mutations and for less frequent mutations, and there is the potential to do deep sequencing. But those analyses have not yet been done.

DR. ROBINSON: Okay. Thank you.

Now, in terms of -- I notice you used the IC95 presumably of wild-type virus for your targeting of your plasma concentrations. What have you found in terms of the stability of -- or the distribution of the IC95s among wild-type viruses and how does that compare to the stability of using

a metric -- a multiple of IC50 or an IC90 in terms of defining your minimum concentration?

DR. CHENG: So I'll ask Dr. White to come speak to that.

DR. WHITE: As the slide comes up, we have in vitro data looking at many different wild-type strains, laboratory strains and clinical isolates in a number of different cell types for elvitegravir. And in those, we looked at the EC50 because it's the most reliable measure of drug susceptibility. And in both T cells and macrophages with both lab and clinical strains that lack integrase resistance mutations, we found pretty consistent low nanomolar to sub-nanomolar EC50 values.

Slide up, please. So on this slide, here are the data showing the different HIV strains that we studied and the different cell types that we studied. For elvitegravir, the integrase inhibitor, the EC50s are shown here. We also determined CC50s which led to high selectivity indexes in these cells.

DR. ROBINSON: So given that the EC50s were relatively -- had a relatively narrow distribution, I'm a little surprised that you chose the IC95 rather than multiples of EC50 for targeting your therapeutic concentrations.

DR. WHITE: The EC95 was derived from the EC50 values that we measured based on the hill slopes that were determined.

DR. ROBINSON: Okay. And then a final question, was there any use of nonclinical data in terms of helping to generate your target concentrations and the appropriate PK metric to look at? And I'm thinking of, for example, hollow fiber monitoring or some other dynamic exposure experiment.

DR. KEARNEY: We did not use preclinical or hollow fiber type of experiments. We used clinical data from those monotherapy studies where we ranged the PK parameters, and then when we identified trough as appearing predictive, then modeled a 20-fold range of observed dosing in patients to trough in the IQ that we wanted.

DR. ROBINSON: Okay. Thanks.

DR. MURATA: Dr. Cheever.

DR. CHEEVER: One of the realities in clinical practice is people often discontinue their drugs kind of on their own for a variety of reasons. And sometimes fixed-dose combinations, if the half-lives are significantly different, it can affect how quickly people develop resistance in that setting.

What are the relative half-lives of the different drugs that are in QUAD?

DR. CHENG: Thank you very much.

DR. KEARNEY: So the half-lives of the components of QUAD are pretty complementary. Elvitegravir's half-life in the boosted state is somewhere between seven to nine hours in patients. FTC is about 10 hours. Tenofovir is about 17 hours. Cobicistat as a mechanism-based inhibitor has a very short half-life, and that's actually desirable.

So relative to Atripla where efavirenz has a very long tail, as it's often called, relative to

the nucs, these are more aligned.

DR. MURATA: Dr. Kuhar.

DR. KUHAR: Back to slide 71 with resistance, it looks from the slide that all of the -- I guess in 102 and 103 that all of the patients that developed resistance to elvitegravir also were resistant to nucleoside class as well. Is this true?

DR. CHENG: Yes, but I'll let Dr. White come speak to that.

DR. WHITE: Slide up, please. Yes, in the integrated QUAD resistance analyses, we found 13 patients who had genotypic and phenotypic resistance to any component of QUAD. Most patients with resistance had the M184V mutation in RT and an elvitegravir primary resistance mutation.

This is not a new finding for this type of regimen, as we found similar frequency and linkage of RT and integrase resistance for QUAD as well as raltegravir plus Truvada, and this has been published in the results of the start Merck (ph) and Qd Merck studies. So it appears to be an NRTI

INSTI regimen-specific effect. However, this resistance that emerged was manageable, and we had good second line regimen outcomes. I'd be happy to share with you more details on those comparisons with the raltegravir studies, if you'd like.

DR. KUHAR: No, I didn't need to do that. I was actually more interested -- do you have any further information on, for example, timeline to developing elvitegravir resistance in the patients that did and also their baseline viral load characteristics?

DR. WHITE: Yes, certainly. What I can show you is a slide showing the specific genotypes that emerged for each subject, each of those 13 subjects and their baseline viral load.

What you'll see on this slide is the genotype shown for the 13 patients. You will see on the left of the slide the specific NRTI mutations that emerged, and that's followed by the integrase mutations that emerged.

Slide up. This is broken down by Study 102 and 103, but totals the 13 patients with any

emergent resistance. And as you can see, there was linkage of M184V with a primary INSTI resistance mutation.

The baseline HIV RNA for these was relatively high. The gray shading indicates a baseline viral load greater than 100,000, and as you can see, 11 of the 13 patients with emergent resistance did come in with that high HIV RNA.

DR. MURATA: Dr. Glen.

DR. GLEN: I was, first of all, wondering do you have any comparable iohexol data with ritonavir?

DR. CHENG: I'll ask Dr. Kearney to address that.

DR. KEARNEY: As was seen with cobicistat, ritonavir had no effect on iohexol clearance in that study. So ritonavir was an arm in that study, and that's when I answered Dr. Estrella's question. We saw less of an effect on eGFR of ritonavir relative to COBI, but neither compound, COBI or ritonavir, affected actual GFR as assessed by actual GFR.

DR. GLEN: But it behaved the same way, so you did see an effect on GFR but not then on with the iohexol?

DR. KEARNEY: No effect on actual, correct.

DR. GLEN: Okay. And do they have quantitatively similar effects on the MATE 1?

DR. KEARNEY: I'll ask Dr. Ray to come up and answer that question.

DR. MURATA: Please state your name.

DR. RAY: Adrian Ray, Gilead Sciences.

COBI and ritonavir both have very similar effects on the MATE 1 transporter as well as other cationic transporters expressed in the kidney that may transport creatinine.

Slide up. This slide summarizes data for cobicistat, ritonavir as well as the prototypical creatinine elevating compound cimetidine and trimethoprim. And as you can see, they are all reasonably good inhibitors of MATE 1, cobicistat and ritonavir both having pretty much the same value in terms of inhibition between a 1 and 2 micromolar.

DR. GLEN: So does that mean there's another mechanism, too, if they're quantitatively similar on MATE 1, but they have differential effects on eGFR?

DR. RAY: There are differences in protein binding that may affect the free concentrations between ritonavir and cobicistat. Ritonavir is more protein bound, and that may affect the levels that are present to inhibit the MATE 1 in the kidney.

DR. GLEN: And then could you or someone else just speak more to the mechanism of the proteinuria?

DR. CHENG: In terms of the mechanism of proteinuria that we've seen to date, I think it's something that we're still looking at right now. I don't think we have a full understanding of that effect.

DR. GLEN: Any hypotheses or?

DR. CHENG: I'll ask Dr. Winston to come speak to that, please.

DR. WINSTON: Good morning. My name is

Jonathan Winston. I'm a nephrologist and a professor of medicine at Mount Sinai School of Medicine. I serve as a consultant to Gilead for the purposes of these meetings and have no financial interest in the outcome of the meeting.

I'm not sure -- could you repeat the question, please?

DR. GLEN: Just some of your leading hypotheses of the mechanism of the proteinuria.

DR. WINSTON: Well, in general, proteinuria is reasonably prevalent in HIV-infected patients. So that's either a mild glomerular disease or a mild tubulo-interstitial disease. Emergent proteinuria in our patients are very, very infrequent. The combination of proteinuria with glycosuria and phosphaturia is often referred to as tubule proteinuria.

So we don't understand the exact mechanism, but the presumption is that there's a certain amount of filtered protein that's reabsorbed or metabolized by the tubule cells, and that's deficient when you have tubule cell dysfunction.

DR. GLEN: I meant have you looked at the drug to that effect?

DR. WINSTON: Well, if the drug is causing proximal renal tubule cell abnormality, then the protein in the urine is in theory a marker of dysfunction of the proximal tubule cells.

DR. GLEN: And can we drill down further on how or what are your thoughts on what it's doing to the proximal tubular abnormality?

DR. WINSTON: We don't -- that's not completely understood. The preclinical data show that the drug has very benign metabolic effects on tubule cells. There are some clinical studies, notably biopsy studies, which indicate mitochondrial dysfunction in tubule cells. So there's some discrepancy between what we know in preclinical and clinical studies, but the mechanism of action is really not understood.

DR. GLEN: Are those mitochondrial abnormalities specific to the proximal tubule cells, or are those seen in other cells, too?

DR. WINSTON: My understanding is that it's

in the kidney reasonably specific to proximal tubule cells.

DR. MURATA: There is one last -- I'm sorry.

DR. WINSTON: I just want to just clarify that's a tenofovir effect, not a cobicistat effect.

DR. MURATA: There is one last person on my list, and that's Dr. Corbett before we break.

DR. CORBETT: I have just a couple of clarifications about some pharmacology information. So the first was, do you guys know if elvitegravir is actually a substrate for PGP or other transporters?

DR. CHENG: I'll ask Dr. Kearney to come speak to that.

DR. KEARNEY: Elvitegravir is not a substrate for PGP or others.

DR. CORBETT: Okay. And then my other question was, do you guys have any information on the prediction of drug-drug interactions with telaprevir or boceprevir?

DR. KEARNEY: Yes, there's a lot of new emerging data on the drug interactions with the PIs

that are somewhat unexpected, and so those data were presented at the CROI meeting earlier this year. So we are now in the process of designing some studies to look at QUAD, COBI with the HCV PIs as well as our own HCV compounds.

DR. CORBETT: And I think my last question wasn't mentioned, but maybe you can talk about this as well. So just to clarify with QUAD and administration of antacids because of chelation effects, it's only an antacid effect. But there are no issues with acid suppression with HT blockers or PPIs; is that true?

DR. KEARNEY: That is correct. The mechanism of action of integrase inhibitors is metal binding domain, and so we hypothesize that we could see that effect. And that's why we conducted the study with antacids which have very high concentrations of dye and trivalent cations, and we saw a reduction in elvitegravir because atazanavir has a pH-dependent solubility. Then the question naturally was, is it a pH question, and so we conducted studies with both PPIs and H2 blockers.

And there's no effect of H2 blockers or PPIs or no pH effect on elvitegravir absorption. It's actually a cationic precipitation in the gut.

DR. CORBETT: Thank you.

DR. MURATA: Based on the interest of time, I will recognize those two questions, but let's start that off in the afternoon session when we have a longer discussion. So we will try to stick to schedule here.

So now we will take a 15-minute break. I have two announcements. One, I've been advised to mention that the FDA slides are now available at the registration desk. And second, panel members, please remember that there should be no discussion of the meeting topics during the break amongst yourselves or with any other members of the audience. And we will resume as scheduled at 10:45 in the morning.

(Whereupon, a recess was taken.)

DR. MURATA: Now we will reconvene the meeting with the FDA presentation.

Dr. Sherwat.

FDA Presentation – Adam Sherwat

DR. SHERWAT: Good morning. My name is Adam Sherwat, and I'll be presenting today on behalf of our multidisciplinary review team. For the sake of brevity for the remainder of this presentation, I'll be referring to the elvitegravir/cobicistat/emtricitabine/tenofovir fixed-dose combination as E/C/F/T.

The current application requests approval for a treatment naive indication based on the 48-week safety and efficacy data from Studies GS-US 236-0102 and GS-US 236-0103. I'll be referring to these studies as 0102 and 0103, respectively.

These are phase 3 randomized, double-blinded, double-dummy active control trials. The control arm for 0102 is Atripla, while the control arm for 0103 is Truvada plus atazanavir boosted with ritonavir. The primary efficacy endpoint was the percentage of subjects with HIV RNA less than 50 copies per mL at week 48 using the FDA snapshot analysis.

Both trials employed a non-inferiority

design with a non-inferiority margin of 12 percent. Both stratified based on HIV-1 RNA level at screening, and both employed virtually identical inclusion and exclusion criteria. A total of 1,408 subjects were included in the pooled intent-to-treat population.

In 0102, subjects were enrolled in 102 sites in the U.S. In 0103, subjects were enrolled in a total of 146 study sites, 88 in the U.S. and all but two of the others in Western Europe, Australia, Canada or Mexico.

Turning to the primary efficacy results, in Trial 0102, 87.6 percent of E/C/F/T subjects have virologic success compared to 84.1 percent of subjects in the Atripla group. In Trial 0103, 89.5 percent of E/C/F/T subjects had virologic success compared to 86.8 percent of subjects in the Truvada plus boosted atazanavir group.

In both studies, the E/C/F/T arm met the prespecified non-inferior margin of 12 percent.

A number of subgroup analyses were performed on the primary efficacy endpoint. No substantive

difference in efficacy based on gender, race, age, region, baseline HIV RNA level or baseline CD4 count were appreciated. However, women comprised only 8 to 12 percent of subjects enrolled across study arms.

My comments will now focus on the virologic resistance profile of E/C/F/T. Twenty out of 24 of the confirmed virologic failure subjects in the E/C/F/T group had treatment-emergent integrase substitutions. Eleven of these subjects had primary elvitegravir resistance associated substitutions. Nine subjects had other substitutions of unknown significance in the HIV-1 integrase. Four subjects had no integrase substitutions.

Of the 11 subjects with primary elvitegravir resistance, 10 of these subjects also had evaluable NRTI resistance data. All 10 of these subjects developed M184-related substitutions. Three of the 10 subjects developed both K65R and M184V substitutions. Of the 13 subjects without primary elvitegravir substitutions, one subject developed

both K65R and M184I substitutions, and one subject developed only an M184V substitution.

In the Atripla treatment arm, eight subjects developed efavirenz resistance associated substitutions, seven with a K103N and one with a K101E. And two of these eight also developed both K65R and M184I/V substitutions.

Cobicistat is structurally similar to the HIV-1 protease inhibitor ritonavir. The applicant showed that COBI does not inhibit HIV-1 protease in a biochemical assay or inhibit HIV-1 replication in cell culture. To assess possible antiviral activity in vivo, we analyzed the protease from virologic failure isolates.

A disproportionate number of protease substitutions developed in the E/C/F/T arm compared to the Atripla arm, 9 out of 14 subjects versus four out of 15 subjects respectively.

Three of the nine protease substitutions and isolates from the E/C/F/T arm have been associated with resistance to protease inhibitors compared to one out of four in the Atripla arm. However, none

of the protease substitutions are considered primary resistance mutations. The clinical relevance of this observation is unclear at this time given the small number of subjects involved.

I would like to turn now to the pharmacokinetic profile of E/C/F/T. Elvitegravir is metabolized by CYP3A4. COBI, a CYP3A4 inhibitor, is metabolized by CYP3A4 and CYP2D6. FTC and tenofovir are primarily eliminated unchanged through the renal route.

With respect to renal impairment, PK data support the administration of E/C/F/T to patients with an estimated GFR greater than or equal to 70 mLs per minute without any dose adjustments. In the setting of hepatic impairment, PK data support the administration of E/C/F/T to patients with either mild or moderate hepatic impairment without any dose adjustments.

Pharmacokinetics in subjects with severe hepatic impairment has not been evaluated. As food increases elvitegravir exposure, E/C/F/T should be taken with food.

E/C/F/T will not be combined with other antiretroviral drugs. Hence, clinical recommendations regarding co-administration are not applicable. Clinical recommendations pertaining to drug-drug interactions of E/C/F/T with non-antiretroviral drugs will be based on the results of drug-drug interaction studies as well as the metabolic properties of elvitegravir, COBI and the administered drugs.

Information to address the potential for drug-drug interactions with methadone, buprenorphine, naloxone, boceprevir and telaprevir was not provided in this application. However, drug-drug interactions are anticipated based on the metabolic properties of these drugs.

In addition, a drug-drug interaction of E/C/F/T with oral contraceptives was anticipated. As such, the applicant conducted a trial evaluating E/C/F/T with Ortho Tri-cyclen Lo or norgestimate/ethinyl estradiol. The results of this trial revealed a 126 percent increase in mean systemic exposure of norgestimate and a 25 percent

decrease in the mean systemic exposure of ethinyl estradiol.

The decreased exposures of ethinyl estradiol are unlikely to compromise contraceptive efficacy. The clinical significance of increased norgestimate exposures and the benefit/risk for HIV-infected women is under discussion. Results from this drug-drug interaction trial cannot be extrapolated to other oral contraceptives.

The remainder of my presentation will focus on the review of safety data. The clinical safety review was based primarily on the data from the two phase 3 trials, 0102 and 0103. As their study design was virtually identical, the safety analysis was conducted by pooling safety data from the E/C/F/T groups, recognizing that integrating data in this fashion does have its limitations.

In addition, results from the small phase 2 trial, GS-US 236-0104, of E/C/F/T versus Atripla provided supportive data. High-level safety data from phase 2 and phase 3 trials with elvitegravir and phase 2 and phase 3 trials with COBI were

reviewed when deemed appropriate.

In the pooled phase 3 analysis, six subjects died during the 48-week treatment period, one in the E/C/F/T group, two in the Atripla group and three in the Truvada plus boosted atazanavir group.

The subject who died while receiving E/C/F/T was a 46-year-old white male with a history significant for major depression, bipolar disorder, insomnia and amphetamine abuse. The subject committed suicide on day 177. His death was judged as unrelated to study drug by the investigator.

The blue and green rows of this table summarize the non-fatal serious adverse events which occurred in the phase 3 studies. The blue row summarizes all serious adverse events while the green row summarizes only the serious adverse events which were judged related to study drug by the investigator.

In the pooled phase 3 analysis, 9.6 percent of subjects receiving E/C/F/T had a serious adverse event compared to 6.8 receiving Atripla and 8.7 percent receiving Truvada plus boosted

atazanavir. Only five subjects in the E/C/F/T group experienced serious adverse events judged related to the study drug by the investigator.

The yellow row of this table summarizes the adverse events which led to discontinuation of study drug. 3.7 percent of subjects in the E/C/F/T group, 5.1 percent of subjects in the Atripla group and 5.1 percent of subjects in the Truvada plus boosted atazanavir group experienced adverse events leading to discontinuation of study drug.

This table summarizes the common adverse events by MedDRA preferred term which displayed a difference of greater than or equal to 3 percent between the E/C/F/T group and either comparator group.

Of the adverse events outlined in the table, headache occurred more frequently in the E/C/F/T group than in both the Atripla and the Truvada plus boosted atazanavir groups. However, 96 percent of headache adverse events in the E/C/F/T group were grade 1 in severity, and only one subject discontinued E/C/F/T related to headache.

The adverse event abnormal dreams and insomnia occurred more frequently in the E/C/F/T group than in the Truvada plus boosted atazanavir group but less frequently than in the Atripla group. However, all of the adverse events in the E/C/F/T group were of mild or moderate severity except for one subject with grade 3 insomnia. No subjects in the E/C/F/T group discontinued study drug due to sleep disturbances. Gastrointestinal adverse events, including diarrhea and nausea, were common in all groups.

As the use of tenofovir has been associated with decreases in bone mineral density, we assessed for evidence of bone toxicity in the phase 3 studies. However, it should be noted that all treatment arms included tenofovir as a component of the study regimen.

The combined frequency of osteopenia and osteoporosis was 1.3 percent in the E/C/F/T group compared to zero in the Atripla group and 2.2 in the Truvada plus boosted atazanavir group. The overall frequency of bone fractures was 1.3 percent

in the E/C/F/T group compared to 1.7 percent in the Atripla group and 1.7 percent in the Truvada plus boosted atazanavir group.

The table summarizes the treatment emergent bone fractures which occurred at anatomic sites associated with osteoporotic fractures. No overall difference in frequency was apparent in the E/C/F/T group when compared to the control arms, and several of these fractures were associated with trauma.

A DEXA sub-study was performed in a subset of 120 patients in Study 0103. The table summarizes the results of the bone mineral density findings at week 48 compared to baseline. There was a decline in lumbar, spine and hip mineral density in both treatment groups with no statistically significant difference in the percentage change from baseline to week 48 between the treatment groups.

The remainder of my presentation will focus on the discussion of renal safety. Prior to discussing the specific safety issues identified in

this application, I'll provide a brief background on tenofovir nephrotoxicity.

The signature profile of tenofovir associated nephropathy is a partial or complete Fanconi syndrome with or without reduction in GFR. Fanconi syndrome is a generalized proximal tubulopathy. In its complete form, it includes renal tubular acidosis, normoglycemic glycosuria, aminoaciduria, hypophosphatemia, hypouricemia and tubular proteinuria.

The tubular dysfunction may proceed the decline of renal function. Proximal tubulopathy may also lead to osteomalacia and decreased bone mass due to phosphate wasting or calcitriol deficiency.

Herlitz et al., presented a renal biopsy series of 13 patients with tenofovir nephrotoxicity. The authors described histological and ultra-structural findings with a distinct pattern of proximal tubular injury characterized by severe mitochondrial damage. Clinical follow-up was available in 11 of 13 patients.

Proteinuria and normoglycemic glycosuria were commonly observed in this cohort. Complete recovery of renal function occurred in only six patients. Five patients exhibited partial recovery but did not return to baseline.

In a case series reported by Malik et al., a similar recovery rate was described. In this case series, only nine patients out of 19 had their serum creatinine return to baseline after discontinuation of tenofovir following the diagnosis of Fanconi syndrome.

Multivariate analysis of postmarketing clinical data have revealed risk factors of tenofovir-induced GFR reduction. These include advanced age; low body weight; higher serum creatinine levels before starting tenofovir treatment; comorbidities, including diabetes, hypertension and hepatitis C co-infection; concomitant nephrotoxic medications; advanced HIV infection; and male sex.

In a separate study by Goicoechea et al., the odds of developing significant renal function

reduction were 3.7 times higher for patients receiving tenofovir plus a ritonavir-boosted protease inhibitor regimen than for those receiving tenofovir plus NNRTI-based therapy, even adjusting for HIV viral load.

The current Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents recommends renal monitoring for all patients receiving tenofovir. Specific monitoring recommendations include serum creatinine and calculated creatinine clearance every three to six months, serum phosphate every three to six months, and urinalyses every six months. More frequent urinalyses may be indicated for patients with increased risk of renal insufficiency such as patients with diabetes and hypertension.

We conducted a literature review to assess the frequency of proximal tubulopathy leading to study drug discontinuation in previous clinical trials using tenofovir as a component of a study regimen in treatment-naive patients.

In the trials used to support the approval of tenofovir in treatment-naive patients, Study 903 and 934, and the trials used to support the approval of rilpivirine in treatment-naive treatments, the ECHO and THRIVE trials, a total of 1,652 treatment-naive subjects received a study regimen which included tenofovir.

No discontinuations of tenofovir due to Fanconi syndrome or due to any other renal adverse event were reported through 48 weeks. Long-term follow-up identified no discontinuations due to renal adverse events through 144 weeks in Study 934 and 288 weeks in Study 903.

I will now focus on the renal issues specific to this application. The applicant maintains that a modest elevation in serum creatinine levels and decrease in estimated creatinine clearance is to be expected with E/C/F/T due to a COBI-related inhibition of tubular creatinine secretion, but that actual GFR is not affected.

This is supported by Study GS-US 216-0121 in

which actual GFR was measured using iohexol after administration of either COBI or ritonavir. Iohexol is a radiographic contrast agent used to directly assess GFR. Using this method, no statistically significant difference in actual GFR were observed in the COBI group at day 7 or day 14 relative to day zero.

It is also supported by comparing creatinine clearance by Cockcroft-Gault with estimated GFR measured by cystatin C in the pooled safety analysis of Study 0102 and 0103. Cystatin C is a low molecular weight protein that is freely filtered by the glomerulus but not secreted by the renal tubules. The comparison of creatinine clearance by Cockcroft-Gault versus the estimated GFR by cystatin C is shown on the following slide.

A decline in creatinine clearance over the course of the trials is demonstrated when calculated by Cockcroft-Gault, as can be seen in Figure 1. However, no decline in estimated GFR is demonstrated when assessed by cystatin C, as shown in Figure 2.

Analogous findings to those in the Cockcroft-Gault analysis were demonstrated for change in serum creatinine. The changes in mean values from baseline at week 48 were .14 milligrams per deciliter in the E/C/F/T group, .09 milligrams per deciliter in the Truvada plus boosted atazanavir group, and .02 milligrams per deciliter in the Atripla group.

I'll mention that the mean change in the serum creatinine at week 48 for the E/C/F/T group plus two standard deviations is equal to .4 milligrams per deciliter. This number, .4 milligrams per deciliter, will be further discussed towards the close of this presentation in relation to renal safety monitoring.

This table summarizes the renal adverse events of all severity grades in the phase 3 trials that fell under a number of descriptive terms. The notable adverse events that occurred with a higher incidence in the E/C/F/T group than in either of the comparator groups included Fanconi syndrome acquired, renal failure, blood creatinine

increased, nocturia and proteinuria.

This table summarizes the serum creatinine and urine protein abnormalities by severity grade. The overall incidence of graded creatinine elevations and graded proteinuria was higher in the E/C/F/T group than in either of the control groups. Seven percent of subjects in the E/C/F/T group had graded elevations in creatinine compared to 1 percent of subjects in the Atripla group and 4 percent of subjects in the Truvada plus boosted atazanavir group.

Forty-nine percent of subjects in the E/C/F/T group had graded elevations in urine protein compared to 29 percent of subjects in the Atripla group and 24 percent of subjects in the Truvada plus boosted atazanavir group. These differences were primarily driven by grade 1 events.

Eight subjects in the E/C/F/T group discontinued study drug to a renal adverse event: three subjects with renal failure, three subjects with blood creatinine increased, one subject with

increased serum creatinine, and one subject with Fanconi syndrome acquired. One subject in the Truvada plus boosted atazanavir group discontinued study drug to the renal adverse event nephropathy toxic.

Four E/C/F/T subjects developed proximal renal tubular dysfunction leading to study drug discontinuation versus none of the subjects in either of the Atripla or the Truvada plus boosted atazanavir groups.

This table summarizes the laboratory characteristics of the four subjects in the E/C/F/T group with renal tubular dysfunction leading to discontinuation of study drug. The laboratory indices of interest will be sequentially highlighted in red on the following slides.

All four subjects developed new onset or significant increases in proteinuria compared to their baseline values, and three of the four subjects developed new onset normoglycemic glycosuria. The values immediately preceding the value in red are the baseline values, and the

values immediately following the value in red are the values at the last available visit.

Only one of four subjects developed evidence of hypophosphatemia around the time of study drug discontinuation, but all four subjects had a substantive increase in their fractional excretion of phosphate.

All four subjects developed an increased serum creatinine which ranged from 1.7 to 4.3 around the time of study drug discontinuation.

The mean age of the four subjects was 41 years with a range of 20 to 60 years of age. All were male, and all were enrolled into Study 0102. The mean baseline CD4 count was 363 cells. Three subjects had a baseline creatinine clearance of less than 90 mLs per minute.

The two subjects who had early evidence of proximal tubulopathy shared the following features: an age greater than 50, a medical history of hypertension requiring antihypertensive medications and a creatinine clearance less than 70 mLs per minute at a screening or baseline visit. Relevant

concomitant medications included oral acyclovir use for 36 days in one subject. Documented nonsteroidal anti-inflammatory use was minimal.

As part of the safety update report, the applicant provided limited high-level safety data from the week 48 analysis of Study 216-0114. Complete safety data from this trial was not provided for review. Study 216-0114 is an ongoing phase 3 randomized, double-blind, active controlled study in HIV-1 infected treatment-naive subjects to evaluate the safety and efficacy of Truvada plus atazanavir boosted with COBI versus Truvada plus atazanavir boosted with ritonavir.

A total of 692 subjects received at least one dose of study drug with 344 subjects in the COBI group and 348 subjects in the ritonavir group. The applicant identified 14 subjects who experienced a renal AE of interest or discontinued study drug due to renal causes, six in the COBI group and eight in the ritonavir group.

We analyzed each case and identified five cases in the COBI group and two cases in the

ritonavir group as being consistent with proximal tubulopathy.

This table summarizes the laboratory characteristics of the seven subjects in Study 216-0114 with renal tubular dysfunction leading to discontinuation of study drug. The laboratory indices of interest will be sequentially highlighted in red on the following slides.

All seven subjects developed new onset or significant increases in proteinuria compared to their baseline values. All seven subjects also developed glycosuria which was normoglycemic in five of the seven subjects. Subject number 9, who did not have glycosuria at the time of discontinuation of study drug, did have one plus normoglycemic glycosuria on an earlier visit.

Four of the seven subjects developed evidence of hypophosphatemia around the time of study drug discontinuation, and all subjects with an available baseline value had a documented increase in their fractional excretion of phosphate.

All seven subjects developed an increase in serum creatinine which ranged from .9 to 5.1 around the time of study drug discontinuation.

Of the five subjects in the COBI group, the mean age was 44 years. Three subjects were male, and two were female. The mean baseline CD4 count was 324 cells, and only one subject had a baseline CD4 count of less than 200. Two subjects had a baseline creatinine clearance of less than 90 mLs per minute, and one subject had a history of type 2 diabetes mellitus. No subjects were receiving nephrotoxic medications.

Of the two subjects in the ritonavir group, both subjects were male and 48 years of age. The mean baseline CD4 count was 432. One subject had a baseline creatinine clearance of less than 90 mLs per minute, and neither subject had a significant past medical history or was receiving concomitant nephrotoxic medications.

This table summarizes the timing of onset of proteinuria and glycosuria in the 11 subjects who discontinued study drug with evidence of proximal

tubular dysfunction in Studies 236-0102, 236-0103 and 216-0114. The first column lists the subject numbers and study groups. Subject numbers 1 through 4 are from the phase 3 E/C/F/T trials while subject numbers 5 through 11 are from Study 216-0114.

The second column lists the study day of drug discontinuation. The third and fourth columns list the first study date when urine protein or urine glucose greater than or equal to one plus was recorded. The final column lists the change in serum creatinine compared to baseline at the time of the first recorded urine protein or urine glucose value greater than or equal to one plus.

All 11 of these subjects developed urinary glucose and/or protein abnormalities that preceded discontinuation of study drug. Eight of these subjects indicated in red had a change in serum creatinine of less than .4 milligrams per deciliter at the time of the first documented urinary abnormalities.

In the phase 3 Studies 236-0102, 236-0103

and 216-0114, 11 subjects discontinued study drug with evidence of proximal tubular dysfunction. This table summarizes these subjects' baseline serum creatinine values, their peak serum creatinine levels while receiving study drug, and their nadir serum creatinine levels following study drug discontinuation. The final column summarizes the number of days between discontinuation of study drug and the reported nadir serum creatinine value.

Ten of these 11 subjects had laboratory follow-up information available after study drug discontinuation. Subject number 9 did not have follow-up laboratory data. In eight of those 10 subjects with available follow-up data, serum creatinine has not returned to the subjects' baseline values at the time of this analysis.

Highlighted in red on this slide is the baseline and nadir serum creatinine values following study drug discontinuation for these eight subjects. Of note, in some cases, the change in serum creatinine may not be the best reflection of change in renal function. As an example,

subject number 8 had a baseline creatinine clearance of 77 mLs per minute, a nadir of 44 and a maximal recovery of 53 mLs per minute.

This slide illustrates that although all subjects showed improvement and often substantive improvement in serum creatinine after discontinuing study drug, the majority of subjects have not returned to their baseline values. However, the follow-up of many of these subjects is still ongoing.

In addition to the applicant's suggested renal safety monitoring plan, the following measures should also be considered: extending renal monitoring to all E/C/F/T recipients, monitoring urine protein and urine glucose, and providing a creatinine threshold to distinguish the effect of COBI on serum creatinine from genuine renal dysfunction.

This latter goal it appears that we have agreement with the sponsor at this time. These measures will be individually discussed in the following summary slides.

We suggest that there may be potential benefits of extending renal monitoring to all patients receiving E/C/F/T as opposed to only monitoring patients with renal impairment or at risk of renal impairment. Renal monitoring is currently recommended for all patients receiving tenofovir for DHHS guidelines.

In the phase 3 Studies 236-0102, 236-0103 and 216-0114, it was not possible to wholly predict who would develop proximal tubulopathy based solely on their risk factors. Eleven subjects discontinued study drug with evidence of proximal tubular dysfunction in these studies. Four of the 11 subjects had a creatinine clearance greater than or equal to 90 mLs per minute at baseline, had no history of either hypertension or diabetes, and were not receiving a ritonavir-boosted protease inhibitor.

The only potential risk factors for these subjects were a baseline CD4 count of 145 cells in one subject and receipt of oral acyclovir for 36 days in another subject. However, the latter

subject had new onset normoglycemic glycosuria, worsening proteinuria, and a serum creatinine increase from 1.1 to 2.0 prior to starting acyclovir.

We also suggest that there may be potential benefits of monitoring urine glucose and protein by dipstick. This is a noninvasive, inexpensive and widely available method. It's currently recommended every six months for all patients receiving tenofovir per DHHS guidelines and more frequently for patients with increased risk of renal insufficiency. Unlike serum creatinine and creatinine clearance, urinary protein and glucose measurements would not be confounded by COBI's impact on creatinine secretion.

In the phase 3 studies, abnormal urinary protein and glucose findings were shown to predate drug discontinuation due to tubulopathy in all subjects and also predate appreciable increases in serum creatinine, for example, greater than .4 milligrams per deciliter, in the majority of subjects who discontinued study drug due to

tubulopathy.

Finally, we suggest that there may be benefits to providing healthcare professionals with laboratory thresholds to help distinguish the expected effect of COBI on serum creatinine and creatinine clearance from that of genuine renal dysfunction.

This could serve two important functions. It could aid healthcare providers in identifying patients with true renal dysfunction and prevent prolonged exposure to drug in the setting, and it could also help prevent unnecessary discontinuations of E/C/F/T related to anticipated laboratory changes.

Judging a patient as intolerant to tenofovir due to presumed renal toxicity and thereby losing tenofovir as a future treatment option is of considerable importance. The selection of appropriate thresholds thus requires balancing these two important considerations.

We suggest that a confirmed change in serum creatinine greater than or equal to .4 milligrams

per deciliter from baseline might be an appropriate threshold to trigger more intensive renal safety monitoring. We define confirmed change as a change that was documented on two consecutive visits.

As mentioned in an earlier slide, 0.4 milligrams per deciliter is equal to the mean change in serum creatinine plus two standard deviations measured at week 48 in the E/C/F/T subjects in the pooled phase 3 trials. In these pooled trials, only 17 subjects or 2.4 percent of the E/C/F/T group had a change in serum creatinine greater than or equal to 0.4 milligrams per deciliter on two consecutive visits. These 17 subjects included all four subjects who discontinued due to proximal tubulopathy.

We suggest therefore that .4 milligrams per deciliter may be a reasonable threshold to discriminate the anticipated effect of COBI from genuine renal dysfunction in subjects receiving E/C/F/T and to trigger more intensive renal safety monitoring.

I would like to acknowledge the

contributions of the entire review team and the team members Dr. Komatsu, Dr. Rhee, Dr. Arya, Dr. Florian and Dr. Zeng who provided the slides for their respective disciplines. Thank you.

Clarifying Questions from the Committee

DR. MURATA: Thank you very much, Dr. Sherwat.

Are there now any clarifying questions for the FDA? Again, please remember to state your name before we speak.

Dr. Ellenberg.

DR. ELLENBERG: So with regard to the renal monitoring, I don't really have any idea how adherent people are to these recommendations in terms of monitoring. So I can't guess that if there were such a recommendation what proportion of people would actually have monitoring according to how it's recommended.

So if you expect that to be extremely high, then my question is irrelevant. But otherwise, I'm curious as to if people were careless and did not do the monitoring, what proportion of subjects

receiving this regimen might you expect to ultimately have a clinically important event that possibly would be irreversible?

Can you make such an estimate? I have a couple of other questions, but.

DR. HUNSICKER: Just in response to that, two of the cheapest things that you can get in medicine are a serum creatinine and a urinalysis with a dipstick. I think that it is highly likely that with appropriate warning that these things will be on a repeated -- virtually everybody on these medicines -- I think that once it's going to be clear that there is an issue of nephrotoxicity, tubulopathy with tenofovir, and I think across the board that it's almost certain that there are going to be fairly well -- now, does that mean everybody? No, there are always people who don't do what they're supposed to do, but I think in the large majority of cases, it'll be followed.

DR. ELLENBERG: Right, so this would not be expected to be a problem that people wouldn't get the monitoring.

Okay. My other question is the two comparative regimens in these studies did not include the other preferred regimen with an integrase inhibitor. And in the sponsor's slides, the only specific problem they listed with that regimen was the two pills a day. The other regimens that were used in these two studies, they talked about the various adverse event profiles that were problems.

So my question to the FDA -- because I don't really -– I'm not familiar with the profiles of these regimens -- is given the renal toxicity of this regimen, do you expect there to be other advantages in terms of toxicities compared to the regimen that they didn't use, the other integrase inhibitor regimen, that might balance the fact that there might be renal toxicity? Or would you expect there to be renal toxicity with that one as well?

DR. LEWIS: Hi, Linda Lewis, Division of Antivirals. I don't think we know that, but we don't -- we would hope that at some point some organization or network might compare the two

integrase regimens head to head. But we don't know that there would be a specific safety advantage of one over the other.

DR. ELLENBERG: Right, but the other one's been out for five years, so you have some idea that safety profile, the other regimens are associated with maybe more rash or the dyslipidemia. Are there -- what are the other safety factors with that regimen that might be --

DR. LEWIS: Raltegravir is pretty well tolerated, and I think we would really have to have a head-to-head trial in order to make any sort of assessment of that.

DR. MURATA: Mr. Raymond.

MR. RAYMOND: Thank you.

In terms of the recommendation for monitoring urine protein and urine glucose, my question is just about what the predictive value of that would be and how that would inform either -- if you found elevations, would it lead to a recommendation for more frequent creatinine monitoring, or what would be the clinical utility

of that in guiding decision making?

DR. SHERWAT: I think you're talking specifically about the urine indices? Yes, so I would break it up and look at urine protein and urine glucose as two separate entities. So for urine protein, you saw in the slides even when you're looking at the comparator arms, that it's not infrequent to see proteinuria to some degree. I think it was up to 20 percent in the comparator arms as well.

So that would be useful, I think, as a warning indicator that something may be going on. Now, what's interesting about that is even though you saw very high levels of that in all -- across the board in the studies, the guidelines, the IDSA guidelines, Infectious Diseases Society guidelines, recommend that if you have a HIV-positive person and you have one plus proteinuria repeated, that person should be evaluated anyway for renal dysfunction. So it's kind of a -- in some ways a non-issue. It would be truly concerning even though we're seeing large amounts of that.

So if you're asking as far as the specificity of the marker, proteinuria obviously is not going to be very specific marker.

Normoglycemic glycosuria is a fairly specific marker. I think there were 25 subjects with normoglycemic glycosuria in the E/C/F/T group, and we had four cases of proximal tubulopathy. So that's a much better marker. But when you look at the slide that I presented, that tends to come up a little bit later -- and usually, proteinuria is kind of -- it seems to be at least in those 11 cases more of a herald marker.

So I would look at these things as more like a warning signal. We talked about a prevention toolbox yesterday. I would think of this as like a diagnostic toolbox, that you have different entities that you can look at, proteinuria, glycosuria, creatinine, that's going to be affected by the impact of COBI in serum phosphate.

So I wouldn't look at any of these as a panacea, but I think taken together, you can build a very good clinical picture to decide who has true

renal toxicity and who may not, who may just have COBI-related effects because it's very difficult to say -- for the individuals, there were eight individuals that discontinued, four that I identified as proximal tubulopathy and four that I didn't.

Well, the four that I didn't, it's hard for me to say definitely that that was all just related to COBI. I can show you a slide that shows you those cases, but some of those effects could be related to COBI. But some of it may be related to de novo renal toxicity related to the medications. It could be related to renal toxicity from an underlying problem like hypertension that progressed during the course.

We had one individual -- maybe I can just show you the slide just to give you an idea for that backup slide. It would be slide 56. So the top four are the other four cases that I was talking about, and it's very difficult to say definitively.

If you look at the case number 15, the

second from the top, the person -- that three plus proteinuria baseline, so could the person have underlying renal dysfunction? Very likely, from some other etiology. And was the progression related to the drug, was it related to the -- the creatinine related to COBI? It's difficult to say.

So I wouldn't -- I'm just bringing this up because I wouldn't discount necessarily the other discontinuations in this study of the eight. We saw basically an 8 to 1 disproportion with renal discontinuations and four with proximal tubulopathy. Four may be related to COBI and may be related to other factors.

DR. MURATA: Dr. Giordano.

DR. GIORDANO: In your presentation, you on slide 46 I think said we should consider extending renal monitoring to all patients receiving this proposed drug.

So what's on the tenofovir label currently? Because presumably, whatever is there is going to just come in as a minimum --

DR. SHERWAT: Right, right.

DR. GIORDANO: -- recommendations.

DR. SHERWAT: So I'll paraphrase, and it would be basically with renal dysfunction or at risk of renal dysfunction. So there's no real guidelines about what constitutes directly -- what constitutes risk for renal dysfunction.

So what I'm saying is that even if you take a pretty broad definition of what constitutes renal dysfunction, I can show you a slide. And there's a lot of things that you could potentially have on this slide that constitute that, but it would be -- I'm sorry --

DR. GIORDANO: So on the product label now for the tenofovir, is there a recommendation that everyone have --

DR. SHERWAT: No, there's not.

DR. GIORDANO: -- periodic screening --

DR. SHERWAT: No, it's only people that have underlying renal dysfunction or at risk for renal dysfunction. So this would be a difference.

Now, that's different than what the current guidelines request --

DR. GIORDANO: I just want to know what was on the label for tenofovir --

DR. SHERWAT: Correct.

DR. GIORDANO: -- and you're proposing that there be a recommendation on this label for a universal renal monitoring?

DR. SHERWAT: That's absolutely correct.

DR. GIORDANO: Fine, thank you.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: I have three questions. For slide 19, you mentioned 120 subjects which included in a DEXA scan study. Were those 120 subjects representative of the remaining participants of the study, and were there actual quantifications of what the bone mineral density changes were over the 48 weeks?

DR. SHERWAT: The Z scores, I'm sorry. Yes, I would defer to the sponsor. I would actually ask the applicant if they would be able to provide that detailed information on the Z scores for the DEXA study.

DR. CHENG: Dr. Estrella, you're asking for

Z scores for the 120 patients that are in the study, or would you like to look at BMD changes by percent thresholds that the FDA used yesterday with tenofovir at the PrEP hearing?

DR. ESTRELLA: Just changes in Z scores. And my other question related to the DEXA studies where the 120 subjects and whether they would be representative of the 1,000 pooled subjects.

DR. CHENG: Slide up, SA-219, please. So this is the change in baseline BMD by Z score by visit, and again, with the studies, it doesn't -- it's not dissimilar to -- hold on a second.

Could we go back, please? 219, about the Z scores. Yes. Thank you.

So the Z scores look similar between the groups as there is no statistical difference in BMD changes between either arm. There are also no changes by Z score.

For the demographics on the 218, please. So the difference in the groups was not that dissimilar to the rest of the study overall, predominantly male and --

DR. ESTRELLA: Great. Thank you.

The second question I had was related to the Study 216-0114. Were you able to review the demographic makeup of the patients included in that particular study?

DR. SHERWAT: No, we were provided with very limited data on that study. It was really high-level safety data for discontinuations and SAEs. So if there's specific questions with that breakdown, I would have no choice but to defer to the applicant because we don't have the information.

DR. ESTRELLA: Okay. And then the other question related to that was I think you'd mentioned fractional excretion of phosphate measured using the subset of individuals who were expected to have proximal renal tubular dysfunction.

Was this measured also in the rest of the participants or just in those particular cases?

DR. SHERWAT: Yes, it was a standard, so they measured serum phosphate, fractional excretion

of phosphate, urine glucose, urine protein, creatinine clearance by Cockcroft-Gault, I think. I'm trying to remember if it was by MDRD as well. They did cyst GFR. So, yes, it was part of the screening for every -- part of the follow-up labs for everyone in the two phase 3 trials.

DR. ESTRELLA: And do you recall off the top of your head if there were any trends in terms of increasing fractional excretion despite normal serum phosphate levels as --

DR. SHERWAT: Yes, I don't have that data, but I'm sure the sponsor has the data for what they saw on the average over the course of the trial.

Were you able to present that for us? It's the fractional excretion of phosphate.

DR. ESTRELLA: Thank you.

DR. CHENG: So, Dr. Estrella, we can address two of your questions that Dr. Sherwat mentioned, the demographics of the Study 0114, the atazanavir cobicistat versus ritonavir study. We can present that at least just on the baseline entry criteria, and then we can address your second question, which

is the fractional excretion of phosphate.

Slide up, please. So these are the baseline study characteristics between the studies. They're roughly balanced as you would expect in a phase 3 study. It's slightly more women in this study than the other study, and the baseline HIV RNA is roughly about the same, around 40 percent greater than 100,000. And the CD4 cell count is a little bit lower, in the 300s.

Second slide, please, the fractional excretion. So this is the fractional excretion of phosphate in Study 102. Fractional excretion of phosphate between the two groups and the median change as well as the inner quartile range over the 48 weeks, we did not measure -- it looks roughly about the same, slightly higher on the QUAD arm, numerically higher.

DR. MURATA: Dr. Hunsicker.

DR. HUNSICKER: Just a comment, if that's correct in using serum creatinine, of course, the creatinine excretion, that will confound that particular calculation because you won't have the

urinary excretion -- secretion of creatinine, so you probably ought to recheck that.

Do you follow what I'm saying? Usually, when you're calculating the fractional excretion of phosphorous, you usually standardize it on creatinine. If you've done this with a true GFR, that doesn't apply. But I'll bet you, you did it with standardizing it on creatinine, in which case you have to adjust for the fact that the creatinine is no longer being filtered -- I mean secreted.

DR. MURATA: Dr. Giordano.

DR. HUNSICKER: What it will do is it will make the creatinine clearance lower so that the estimated filtered amount of phosphorous will be lower so that the amount that appears in the urine will appear to be higher fractionally.

DR. GIORDANO: So they'll look worse than they really are.

DR. HUNSICKER: Pardon?

DR. GIORDANO: They'll look worse than they really are.

DR. HUNSICKER: Well, it'll look higher,

yes. That's worse. But if you go back there, that's exactly what you see, and that's what I'm suspecting is that that difference in the -- which is not statistically significant in any case, but the numerical elevation of the fractional excretion of phosphorous seen in the patients who are on QUAD may well be because the secretion of the creatinine was reduced.

DR. CHENG: Slide up again, please, so we can clarify for the committee. Study 102 looks slightly higher, and then could we also in a minute have Study 103 so we could share both slides with the committee?

So within the two studies, roughly about the same response. I will check, confirm on the methodology of what we did. You're probably correct, but I will confirm at the break.

No other questions?

DR. MURATA: Dr. Estrella, are you done?

Dr. Wood.

DR. WOOD: My question is regarding slide number 44. This is a general question as well as

to the nephrology experts who are with us on the panel.

So since we have these 11 individuals, one of them doesn't have follow-up. So actually, 10 out of 10, which is 100 percent, have creatinines that have not returned to baseline. The range is 25 days to 439 days. I'm guesstimating that the mean may be around 68 or 70, and the median may be 40 to 50.

One thing that I'm curious about is that is there any known or given parameter in terms of recovery of renal function. So if you see the kinetics of normalization of creatinine like within 30 days, the likelihood is, is your creatinine is going to become normal. But if you don't see normalization of creatinine by 60 days or 80 days, then there is a higher statistical probability that you're going to go on to have a greater likelihood of permanent renal dysfunction.

I know this may vary according to agents and so forth, but I guess it's just what's known about the recovery and the normalization of renal

function and the implications for if that function is delayed, that that is a greater likelihood that there is permanent renal dysfunction.

DR. MURATA: Dr. Hunsicker.

DR. HUNSICKER: Let me take a stab on this. Actually, I was going to do a disquisition on this sort of issue later on, but you've maybe it a little earlier.

First of all, to answer directly your question, I don't know of any evidence, any data, that relates to that kind of tubulopathy, so I can't really speak to that. But I can say that maybe you can compare this with acute interstitial nephritis, which is something that happens with all sorts of different drugs.

The rate of recovery typically is you get pretty much, let's say, halfway back down to normal in two weeks and maybe in four weeks, you're somewhat closer. And by the end of a couple of months, you should really pretty much be completely clear, if that's all that there is.

Now, I think the more important question is

what is the implication if you wind up with a modest reduction in renal function. And there are two issues here. One is, does that mean that you're more likely to progress. The second is what is the implication if you don't progress, if you just simply stay with a somewhat lower GFR than you would have had in the other.

Now, there is in my community an unfortunate assumption that if you have renal damage that that in itself predisposes to additional more renal damage. Actually, there is not a shred of evidence behind this particular hypothesis, and I've done two studies both in MDRD study and in the other showing that there is absolutely no relationship between baseline serum creatinine and the rate at which creatinine changes over time.

So that I think that the hypothesis that the damage that is there is necessarily going to produce further damage is nonexistent. So there are two things that you can say. Well, okay. People who have HIV are, as you all know, at risk of developing renal damage. Does it make it worse

to have a second cause of damage? Of course it does. But I would say that if you've got HIV nephropathy, that the outcome is so lousy anyway that it probably doesn't make any difference if you start at marginally different levels of renal function.

Does it make any difference to have slight renal insufficiency compared to non-renal insufficiency in terms of renal outcomes? Probably not.

Does it make any difference in terms of cardiovascular? And this is an area of great deal of interest in my community, and, of course, the answer is that renal insufficiency is clearly associated with increased cardiovascular disease, something which incidentally is also increased in patients with HIV/AIDS.

But predominantly, this is when renal insufficiency drops into what's called stage 3, which would be a GFR less than about 60. So that I think that modest changes in the long haul in people who start out with normal renal function

will probably have relatively minor impact so long as they are not progressive.

Now, that means you have to make the assumption that when you stop the agent, that you do, in fact, not have further damage. And I think that that is by and large supported by the evidence that we've seen. There's a tendency to recover, and it doesn't appear that there's late damage.

So I think that a modest amount of loss of renal function -- to answer what I think is your real question, Dr. Wood, a small amount of renal function starting from relative normal probably is associated with minimal long-term adverse outcomes.

DR. ESTRELLA: I just wanted to add that, at least based on observations, the earlier the serum creatinine elevation is detected, the better the outcome in terms of renal recovery. So that's one thing just to comment on.

DR. SHERWAT: The only thing that I would say related to that is on slide 21, these were the two case studies that I looked at where the rates are about 50 percent for recovery, and the recovery

rates for the Herlitz case, they were substantial recovery. And I used that as actually one of criteria when I looked at the Fanconi cases here to see if they were related to drug because you do expect to have a nice general improvement, if not reaching baseline, with removal of study drug.

DR. MURATA: To focus the questions on the clarifications, Dr. Wood, do you have any additional questions for the agency's analysis?

DR. WOOD: No, I don't. Thank you.

DR. MURATA: Well, if there are no additional hands or questions, then we will now break for lunch. We will reconvene again in this room in one hour or 1:00.

I am asked to announce the following. Please take any personal belongings you may want with you at this time. This room will be secured by the FDA staff during the lunch break, and we will not be allowed back into this room until we reconvene.

Panel members, please remember that there should be discussion of the meeting topic during

the lunch amongst yourselves or any other member of the audience. Thank you.

(Whereupon, at 11:48 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:03 p.m.)

Open Public Hearing

DR. MURATA: Why don't we get started to stay with the schedule? So if everyone can please return to their seats.

So we will begin the open public hearing portion of this meeting. Both the Food and Drug Administration or the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's

payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in the consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for the cooperation.

Now, I have been advised that speaker number. 1 is not present. So will speaker number 2 step up to the podium and introduce yourself?

DR. DRISCOLL: My name is Jim Driscoll. I'm with the AIDS Healthcare Foundation. I have no financial connections to Gilead or its competitors. I'm a long-time AIDS activist. I was involved in organizing demonstrations to move the approval of drugs through FDA back in San Francisco in the early '90s. I've not dealt with FDA for a long time. This is a first in more than eight years.

The HIV virus engenders its own peculiar healthcare ecosystem. Here the survival of HIV patients depends on access to quality ARV treatments. HIV patients like members of an endangered species are vulnerable to imbalances in their healthcare system.

When the food supply of an endangered species is diminished, some will perish. Similarly, restricted access to HIV treatment means that some patients will grow sick and die. Introducing any new HIV drug can throw the

healthcare ecosystem out of balance. QUAD, for example, lacks superior efficacy to existing treatment, but its one-dose-per-day convenience may improve patient adherence and thereby improve health and save lives.

Even so, QUAD and other newly introduced drugs can create imbalances in the healthcare system when they divert limited resources from lower-priced regimens into higher-priced regimens.

FDA is authorized to approve this safety and efficacy of new drugs under its mandate to protect and promote public health. Pricing lies outside of its FDA jurisdiction. However, in a system where funding is limited, pricing can create healthcare imbalances that harm public health. Similarly, if high drug costs disproportionately impact minorities, women and other groups, drug pricing can raise civil rights issues.

The HIV community is increasingly worried about high ARV regimen costs creating healthcare imbalances that reduce treatment access. Reduced access here in America is compelling AIDS advocates

to rethink the rules on HIV drug pricing and conclude the following.

First, because of governmental constraints, fiscal constraints, that are unlikely to abate any time soon and may worsen, newly introduced HIV regimens need to be cost neutral to ADAP and other funding streams.

Second, to keep regimens and cost neutral, QUAD must be priced no higher than the main drug it will replace, Atripla, for WAC, ADAP and other pricing structures. Third, PAPs or patient assistance programs are no substitute for ADAP. They are not patient or doctor friendly compared to ADAP. Hyped often as instances of public spirited generosity, they are in reality a corporate tax break windfall. The only true generosity is affordable drug pricing.

These ideas represent a paradigm shift on pricing new HIV drugs. Until recently, the AIDS community was willing to accept a higher price for a new drug if superiority in efficacy and toxicity or convenience could be demonstrated.

However, with current static government funding, higher costs for a new regimen exacerbate imbalances in healthcare. More patients will be forced into ADAP waiting lists, patient assistance programs or worse, left without treatment. Disadvantaged groups will suffer most.

We ask you, do not higher drug costs that reduce treatment access undermine FDA's mandate to protect public health? It's something we all need to think about, particularly the sponsors. Thank you.

DR. MURATA: Okay. Thank you very much.

Will speaker number 3 step up to the podium and introduce yourself?

MR. KING: My name is Jason King. I represent AIDS Healthcare Foundation, and I'm a shareholder with Gilead Sciences.

I'd like to first congratulate President Obama for listening to the gay community this week. I think the advisory committee should have taken out a page from his playbook yesterday when it glibly voted to support a dubious prevention

method.

Testimonials on risk compensation, cost and toxicity were all but ignored. The committee and the FDA should listen to the AIDS community which was broadly represented in yesterday's proceedings.

I realize the FDA's function is to review and assess the safety and use of foods and drugs to be consumed by the public. But as my colleague so eloquently explained before me, the FDA's mandate is to promote and protect the public health. Pharmaceutical companies historically maximize patent life and prolong market dominance, a practice that does not serve the interests of patients or the public health.

I want to take this opportunity to stimulate some thought among the members of this committee and everyone here today. When considering QUAD approval, the committee should think about several things. I am HIV positive, and I take Truvada. We know that Truvada, a component of QUAD, causes damage to vital organs after long-term exposure. We know many patients suffer from these

complications, and those side effects delineated in the package inserts, they're real.

Let me just share a few of them with you. Abnormal skin sensation;, back pain; cough; darkened skin color on the palms of hands, soles or feet; diarrhea, dizziness; gas; headache; indigestion; joint pain; loss of appetite; nausea; sinus drainage; strange dreams; sweating; tiredness; trouble sleeping; vomiting; weakness; weight loss.

Severe problems include bone pain; chest pain; depression; muscle pain or weakness; persistent dizziness; shortness of breath; kidney problems; symptoms of lactic acidosis; yellowing of the skin or eyes; et cetera.

I've been taking Truvada for six years, and I experience a variety of these conditions. Several times a week, it takes me two to four hours to fall asleep. Then I dream strange dreams all night. I dream every night, waking up sweaty, unrested and exhausted. Then the morning greets me with diarrhea. I normally have to stick around a

bathroom most of the day. I have periodic muscle pain and fatigue. It impacts my workday. You can see where this story goes.

Well, I'm not going to die, right? Sure, but is that a justification to not make new drugs that improve the quality of my life? Why not create a drug that not only benefits me but also society and the economy, one that makes me more productive by experiencing fewer side effects or none at all, or better yet, why not truly focus on finding a cure?

Truvada's patent will expire in five years. However, to ensure the profitability of Truvada, it is being incorporated into a new drug dubbed non-inferior to Atripla. Many expect QUAD to be priced high. The AIDS community will not accept this. AIDS programs and other payers are cash strapped and cannot absorb higher drug prices for new AIDS drugs, particularly ones that do not provide superior clinical benefit.

If a drug creator wants to price their drugs high, maybe the community would accept this if the

drug created demonstrated an overwhelming advancement which saved lives and spared the patients from the daily impact of side effects, a breakthrough therapy with no toxicity.

The FDA was installed to, among other things, protect citizens from the excesses and abuses of the pharmaceutical companies. The FDA has failed in fulfilling its mandate time and again. It has become more focused on protecting the pharmaceutical companies from oversight, criticism and lawsuits. This body will likely support Gilead's QUAD, and the FDA will likely approve it. But the administration should consider adopting the function to promote the value of a drug company that genuinely wants to create a cure for AIDS, not simply repackage old goods. Thank you.

DR. MURATA: Thank you.

Now, my understanding is that speaker number 1 has entered the room. Please step up to the podium and introduce yourself.

MS. DEE: Thank you. My name is Lynda Dee,

and I wear a number of hats. I'm from AIDS Action Baltimore and the AIDS Treatment Activist Coalition and the Fair Pricing Coalition. And AIDS Action Baltimore and ATAC have received grants from Gilead and other pharmaceutical companies. Neither Gilead nor any of their competitors have paid my way here. I actually drove from Baltimore.

So I believe that the QUAD should be approved. I think that the sponsor has demonstrated non-inferiority in its pivotal trials, and safety was similar across all arms except disproportionate number of renal events, including proximal tubular dysfunction. And renal toxicity should obviously be addressed in the label.

Regarding the risk/benefit ratio, I believe that the benefit of one pill per day and its positive effect on adherence outweighs the risk of the renal toxicity that we've seen thus far. But I think that a recommendation for kidney function monitoring for all patients should be included in the label since two components of the QUAD present potential for renal toxicity and because more than

one kidney toxicity might be involved here.

I think it's better to be safe than sorry, and until what's actually going on here can be described more fully. I also think that laboratory parameters should be provided in the label to assist physicians in avoiding renal toxicity.

As far as postmarketing trials are concerned, I would obviously like to see more data on exactly what renal toxicities are afoot here.

Secondly, only 8 to 12 percent of trial participants were women, yet another abysmal record of women in pivotal trials. We've seen this time and time again over the years, and frankly, I'm just kind of sick of sitting up here saying the same thing in all of these hearings. I think it's imperative that the agency mandate that the sponsor conduct postmarketing trials to ascertain efficacy and safety in a significant number of women. Unless sponsors are forced to do these kind of trials in women in phase 4, they will never do what is necessary to include significant numbers of women in phase 3.

Gilead did not conduct drug-drug interaction studies with either methadone or buprenorphine. This is also completely unacceptable. I can't imagine that at this time. The panel should definitely recommend that Gilead conduct QUAD DDI studies with methadone and buprenorphine and should also require more DDI data with oral contraceptives as well as DDI studies with boceprevir and telaprevir and other HCV direct-acting antivirals that are close to approval, including the sponsor's 7977, BMS 79052 and TMC 435.

Over the years, I've been a member of quite a few advisory panels, and I know your role here today is to decide whether to recommend the QUAD for approval and not pricing issues. Nevertheless, I think this is an appropriate forum to bring up pricing issues because exorbitant drug prices have created a public health crisis emergency, and shining a light on it at this hearing is a good way to bring attention to this fact, to bring attention to the unconscionable cost of prescription drugs and unreasonable price increases.

Now, my husband died from AIDS complications in 1987. My organization, AIDS Action Baltimore, is commemorating 25 years of service this year to the HIV/AIDS-affected community. I can remember when there were no AIDS drugs. I can remember when people had to take AZT three times a day, and they used to have those little pill boxes where the alarm went off to say it's time to take your medicines when people got up in the middle of the night to take medications. I remember the drugs that came after, with food, without food and the hours in between and all the rest.

Obviously, these fixed-dose combinations are important, and they are an important advance. But I wonder in light of the financial crisis that's already been described here today, what's the risk/benefit ratio in this area? How much really more money or bang do we get for the buck by even more expensive drugs?

The cost of healthcare is completely out of control in this country, and exorbitant prescription drugs have definitely contributed to

this crisis. ADAPs across the country have had waiting lists of over 3,000 to up to 9,000 people in the United States of America. That's outrageous.

Private insurance coverage has also been affected. Many people now have to pay co-insurance, outrageous deductibles and as well as co-pays. Yet prices continue to increase and climb higher and higher.

Gilead's history of price increases is one of the worst with increases of 140.6 percent on the price of Viread since it was approved in 2001. That's an annual price increase average of 13.4 percent.

Is that five minutes?

DR. MURATA: That is five minutes, and that is the time --

MS. DEE: I mean, I have two more paragraphs left since we only have three speakers and you've allotted so much time, can I finish?

Clarifying Questions from the Committee (con't)

DR. MURATA: I'm afraid I can't. Everyone

has five minutes, so I will now proceed with the remainder of the meeting. Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

Now, at this stage, I'd like to address two outstanding issues. One, the sponsor has requested an opportunity to address the questions that were posed by the panel members, and I think this is an appropriate time to do so. And then, second, there are two panel members who were left out of this morning's clarification opportunity from the sponsor, and I would like them to have an opportunity to ask their questions for the sponsor.

So if the sponsor may do so.

DR. CHENG: Thank you, Mr. Chairman.

So there are a number of things that were raised prior to lunch, and I just wanted to address them as we've come back.

So the first of which is, Dr. Hunsicker, you made a comment about fractional excretion of phosphorous and how we calculated that. You are

correct that we did not correct for that factor. So as a result, the data that we did show on those two slides was an overestimate of the fractional excretion of phosphorous. So the reality would be that if calculated more appropriately, they would be closer to the -- the difference would be smaller.

The second issue is the regimens. In discussing the patients who discontinued, the nine patients who did discontinue, it was noted that all of the patients returned to baseline as we had follow-up.

So when we would look on the follow-on regimens, although we do not have follow-on regimens for all nine of the patients, for six of the seven that are available on this slide, they're on regimens that include either ritonavir or there's one on rilpivirine, both of whom have an increased elevation in serum creatinine. So that may contribute a factor, although not necessarily entirely to the fact that they don't return to baseline. So I wanted to share that with the

committee.

Dr. Wood, you had a question -- XX-5, please -- regarding the gender and race of all nine patients that discontinued, and I can address that now. I only knew the four at the time, which were white men.

So of the nine patients that discontinued, seven were white, one was Asian, and one was mixed race. The majority were women. There were two women involved.

Lastly, Dr. Giordano, you made a question about what amount of monitoring is recommended in the current Viread label, and I just wanted to clarify what it currently says -- XX-10 up, please -- which is that in yellow, it's recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy.

So we interpret this to mean that there is monitoring ongoing during -- already for Viread and not just in patients with renal impairment. We don't dispute. We agree with the FDA that ongoing

monitoring should be for QUAD, so just as a clarification point. Thank you.

DR. MURATA: Thank you.

Now I would like to provide the opportunity for Dr. Vega to first ask her questions to the sponsor, if there were any leftover questions from this morning.

DR. VEGA: Hi. I'm Marlena Vega, yesterday's old lady from the birthday, and I found out we have another birthday right over here, so three days ago. So this is the senior set on this side, okay, the 70s-plus side which means that we're integrated.

I'd like to make more of a comment than a -- or an observation, and I think it's a very relevant one. I like the Rose and Gilead organization. I don't know if you know about it, gentlemen and lady. It's in New York, and it talks about -- it's a minority organization, a black organization, primarily with some Latinos, that deals with AIDS patients. And it's actually a very lovely organization. And I'm sure if you contacted

them and wanted to give them a contribution, they'd be very willing, though, in fact, I don't know that.

That's not what I wanted to say, though.

DR. MURATA: Okay. All right. Dr. Vega, I just want to ask you to for the clarifications --

DR. VEGA: Okay. What I want to talk about, though, is mental health, and since I'm the only mental health practitioner here, I would like to say that the gentleman who was very nameless in the suicidality issue, one of the people, he wasn't white. He was Latino and white. His name was Jose. He had a Latino lover and an Asian girlfriend at times. He had a face. He had a body. He was a human being.

You mentioned 9 percent of people who have depression. Okay? And that was in the study, and I'm wondering how that's addressed because I really believe that with my patients that people who are depressed do not do well with their treatment regimen and that it can be, in fact, interrupted. I believe in a mind and body dialogue, and I

believe that the mind helps the body to heal because you don't heal in a vacuum.

And I'm wondering if it's ever going to be or be part of the assessment to have some kind of clinical evaluations for depression, the effect of them, and perhaps the idea that they may, in fact, be very important to understand the interaction between the drug and, in fact, the state of the human being because depression seems to be quite prevalent in our clients. Thank you.

DR. MURATA: May I ask the sponsor to try to address some of the clarification questions? My interpretation would be perhaps the review of the demographics, so the patient population with underlying psychiatric illnesses, including depression, if that's okay with Dr. Vega, and relevant drug-drug interactions between the components or the QUAD itself and any psychiatric medications.

DR. CHENG: Okay. Thank you for that. If we could have the slides, we're going to review in the demographics for Studies 102 and 103 from the

core set. This is reviewing the demographics for the sex and race ethnicity for those involved in the QUAD program by treatment arm between the active -- the Studies 102 and 103 for QUAD and then combined predominantly male and predominantly white with 25 percent black or African American heritage being the second category, 20 percent Hispanic or Latino ethnicity.

DR. VEGA: I'm wondering in the future about getting some more women of black and Hispanic background into your clinical trials. I'm wondering if you're pursuing that because I think that would really be important. I mean, I recognize that women in Botswana are very relevant but not necessarily to women here, who might have a very different point of view and cultural diversity and sensitivity. So I think having more people in the study would be wonderful.

DR. MURATA: I would ask that those points be deferred to the discussion section later today. I think those are relevant points, however.

Lastly, I wanted to provide Dr. Wood with

her opportunity for clarifying questions to the sponsor.

DR. WOOD: Thank you. Lauren Wood. The only clarifying question I had is the safety data is through the end of December of 2011. I'm just curious. What is the median on-study duration for that data cutoff? Do you know how long people have been on study with that cutoff of December?

DR. CHENG: Sixty weeks.

DR. WOOD: Sixty weeks. Thank you.

DR. CHENG: That's the median.

DR. WOOD: Thank you.

DR. CHENG: Mr. Chairperson, did you have questions about drug interactions? Was that one of your other questions --

DR. MURATA: Yes, I wanted to try to extrapolate on Dr. Vega's question about psychiatric illness and depression. If there are any data from the relevant QUAD studies about drug-drug interactions that may be of relevance to her point about drug-drug interactions of psychiatric illness, the medications used commonly

in psychiatric illnesses.

DR. CHENG: I'll ask Dr. Kearney to come speak to that.

DR. KEARNEY: I think we would echo your comments that it's very important to provide guidance for the use of psychiatric medications, and they can have a variety of different metabolic pathways. I shared with you very high-level data or information about what we plan to have in the prescribing information, but please know that we do have very specific recommendations based on the known metabolic pathways of the medications as well as the effects that our compounds can have to provide clear guidance.

DR. VEGA: Thank you. I'm really happy to hear that because when I'm with a patient and they're taking so many different medications, very often they leave out the psychiatric medication. They say, well, I can't take everything because it might counter-indicate. And then, in fact, what happens is they are insomnolent and they have other issues. And in bipolar disorder, which is the

majority of my patients, it really has quite a negative side effect as you can well imagine.

I would imagine that having some kind of a clinical understanding of this is just really truly important. Even though I know I'm a pain in the neck, I think it's really important.

DR. CHENG: Thank you for that. I did want to add that we do have an approved all women's study in antiretroviral-naive patients. That already has IRB approval. It will be the first of its kind.

Mr. Chairman, would it be okay if I showed that slide, or would you prefer to defer that?

DR. MURATA: At the moment, I would prefer to defer that because I think that may lead into some of the points that have listed for discussion, if that's okay with the agency.

DR. LEWIS: I think that this might be an appropriate time to ask the applicant to share any information they have about any postmarketing studies that are already planned. This may be as good a time as any.

DR. MURATA: I think that sounds reasonable.

DR. CHENG: Then I'll proceed.

Slide up, please. So this is Study 236-0128. This is a randomized, double-blind, active controlled study in treatment-naive women. And this is being conducted in the United States, and it's very similar to the 103 study in that it's fully powered. And we're looking at a 48-week study which will be 100 percent women.

This is the first of its kind in HIV clinical trials that I'm aware of that's this size and all women, and we are well along our way. We have a CRO, and we have our central IRB approval for the study already. And we're working with some of the centers obviously that focus on recruiting women because that's -- it'll be different center mix than what we currently have in Studies 102 and 103.

DR. VEGA: Better.

DR. CHENG: In terms of the other phase 3b/4 studies, we have two other trials -- or three other trials that are ongoing. This is a phase 3b

study that looks at patients that are stably suppressed on a ritonavir-boosted protease inhibitor, and we randomized to switch in 2 to 1 fashion onto QUAD or remain on their boosted PI. This is a two-year study with a primary endpoint at week 48. This is ongoing already. We have roughly 115 patients already enrolled in this trial.

We have a similar study which is Study 121, which is for patients who are on -- stably suppressed on a nucleoside-based regimen. And they will be randomized again 2 to 1 to switch onto QUAD or remain on the current therapy. Thank you.

DR. MURATA: Is that sufficient for the agency, discussion for the studies?

DR. LEWIS: Did you have any ongoing or in progress drug-drug interaction studies that you could share?

DR. CHENG: We should also mention that we have a renal impairment study that's ongoing right now. Study 118, please. This is a two-arm study looking at patients who are treatment-naive to therapy. And they have GFRs in between 50 and 90,

and they'll either be -- the treatment-naive patients will in an open label fashion begin on QUAD, those who are stably suppressed on a boosted protease inhibitor and two non-nucleosides -- two nucleosides, will swap out ritonavir for cobicistat in this study.

This study began enrollment last fall with roughly 80 people of the 100, so we're 80 percent enrolled in this trial. We are looking at additional -- we're looking at other theoretical or investigational markers of tubulopathy in this study that's ongoing.

DR. MURATA: It looks like we are ahead of schedule before the charge to the committee. There appears to be several hands going on probably relevant to some of the clarification points. So let me go down the list of hands that have been raised.

DR. KEARNEY: Mr. Chairman, I'm sorry. May I just finish?

DR. MURATA: Yes, please. I'm sorry.

DR. KEARNEY: I'd just like to clarify. The

agency mentioned in their presentation that we had conducted a methadone and buprenorphine study. It is correct we had not completed that study in time for the NDA filing, but that study has completed. The agency has not received it yet. It has not reviewed it yet.

The top-level data is that there are no clinical significant interactions with either methadone or buprenorphine based on PK or PD assessments in those studies.

DR. MURATA: Is the sponsor done?

DR. CHENG: Yes.

DR. MURATA: All right. Thank you.

Then let me go down the list. Dr. Corbett, you had a question?

DR. CORBETT: I actually found the answer to my question. Thanks.

DR. MURATA: All right. Thank you.

Mr. Raymond.

MR. RAYMOND: Just along the lines of the planned or underway drug-drug interaction studies, could you address the question that was raised in

public comment about contraceptives?

DR. CHENG: I'll ask Dr. Kearney to come respond to that.

DR. KEARNEY: As reflected in the background packages, we did conduct a study with a representative oral contraceptive. We saw a small decrease in the estrogenic component, and we did see the increase in the progestin component. I think, like the agency, we have struggled to find data in the literature, specifically what the implications for that can be.

Our recommendation in the file was to mirror that boosted atazanavir which had similar observations. But we are looking forward to working with the agency to determine exactly what information and what recommendations to provide on product labeling as it relates to those data.

DR. MURATA: Okay. Dr. Corbett, is this relevant --

DR. CORBETT: Could I just ask for clarification relevant to that issue?

DR. MURATA: Yes.

DR. CORBETT: Did you guys look at progesterone at all, or did you plan to look at progesterone in those people as a marker?

DR. KEARNEY: Is your question specifically another study that would look at just the progesterone?

DR. CORBETT: No. Within that study, are you able to look at progesterone levels of those people as a marker of ovulation?

DR. KEARNEY: So we did look at LH and FSH hormone in that study. We saw no changes. So I think the unresolved question is the potential clinical implication of the higher progestin, administered progestin component.

DR. MURATA: Dr. Glen, did you have a question or -- okay.

Dr. Daskalakis.

DR. DASKALAKIS: Just a question about the studies that you showed, the women's study, is it domestic or international or both?

DR. CHENG: All the study sites have not been fully selected yet, but it will primarily be

in the United States. It's likely to be some Western European involvement, but we imagine that the core of the study will be conducted in the United States.

DR. DASKALAKIS: That's great. Another question about the SWITCH study from a stable PI to the QUAD. Is the PI their initial regimen, or could it be a salvage regimen?

DR. CHENG: It will be their initial regimen.

DR. DASKALAKIS: Good. Thank you.

DR. MURATA: And Dr. Hunsicker, thank you for your patience.

MR. HUNSICKER: Very quickly about your renal impairment study that you just told us about, if the admission criteria is that the estimated GFR has to be above 50 but you also have to, according to your label, stop the stuff if the GFR is below 50, and you know that the likelihood is that the eGFR is going to fall, you're going to run into some troubles there.

So how have you -- is this just an

oversight, or have you adjusted the rules for stopping when the person's GFR drops below 50? How are you handling that?

DR. CHENG: We do not have the same rules in this study because we're not solely using Cockcroft-Gault as the only measure of GFR in this trial. We're also collecting cystatin C. We're also looking at CKD-EPI as well as MDRD to look at for this --

DR. HUNSICKER: Well, MDRD will give you the same thing as any other creatinine-based formula.

DR. CHENG: I understand, but we're looking at a variety of different --

DR. HUNSICKER: Sure. Nonetheless, if they come in at 50 and if your rule says that if they drop below 50, then just simply by random fluctuation, you're going to have a substantial number of people dropping out for non-changes.

DR. CHENG: Correct, and -- but we find that in some laboratory -- in fact, I just dealt with a case like this, this morning, is that we have patients who have GFRs that may be dropped, but

there's differences when you look at the other monitors, when you look at cystatin C, for instance. And we're using that to adjust monitoring as well.

DR. HUNSICKER: I didn't hear what you said, but you have enough room so you're not going to drop people out for nothing?

DR. CHENG: Correct.

DR. HUNSICKER: Okay. Thank you.

DR. MURATA: Could I ask as the chair's prerogative for the sponsor to put up the schematic for the renal impairment study again?

DR. CHENG: I'm sorry. You'd like to see it again?

DR. MURATA: Would you mind putting up the schematic for the renal impairment study?

Dr. Estrella.

DR. ESTRELLA: So I guess following up on Dr. Hunsicker's question, what is the cutoff GFR at which you would take the participant off in the GFR impairment or renal impairment study?

DR. CHENG: Once it's below 50, there's a

discussion between the physician and the sponsor, and we're looking at that carefully.

If I could show the previous data, please, that was on the backup slide. Let me give you -- SA-86 up, please.

So in this example, these are the -- at the time of the data cut, this is a small number of patients, but you can see that they -- cystatin C GFR does not always mirror what we see with Cockcroft-Gault, as you know. And so I think we're looking to see that -- the hypothesis is that there could be in patients with GFRs between 50 and 70, that perhaps cystatin C is a more appropriate measure.

DR. HUNSICKER: I think that it's entirely appropriate to study the patients with renal insufficiency. Don't misunderstand me. I just think that if you don't have a very clear boundary below the admission value before they drop out, you're going to lose half your patients because just simply on random fluctuation, half of them are going to fall below 50.

DR. CHENG: We do. The percentage is 25 percent.

DR. MURATA: Are there any other clarifying questions to the sponsor or perhaps to the agency amongst the panel members?

Dr. Estrella.

DR. ESTRELLA: I have one more question. Which cystatin C GFR equation are you basing the GFR cyst C on?

DR. SZWARCBERG: We'll have to get back to you on that question. We'll look into it and get back to you during the course of the discussion, if that's possible.

DR. MURATA: Okay. Well, if there are no further clarifying questions, I suppose we will ask the agency to proceed now with the charge to the committee.

Charge to the Committee – Linda Lewis

DR. LEWIS: Thanks, Dr. Murata.

We really appreciate the advisory committee's attention to the details of these study presentations and our review presentation. The

public discussion of new products is an important part of FDA's review process.

I should always state that the FDA believes that new treatment options are always needed, and they provide patients with choices because we know that not all patients do well on the same drugs.

You've heard presentations today describing the efficacy of the elvitegravir-based fixed-dose combination product. In two comparative studies, the E/C/F/T has produced high levels of virologic suppression. Not too many years ago, these levels of virologic success would really have gotten a lot of positive attention.

You've also heard presentations summarizing the safety profile of the FDC product. And so as part of your charge, we would ask you to look at all of this data and reflect back on your assessment of the safety profile and the risk/benefit of this product in a treatment-naive population.

The voting question will obviously be, do you believe the data support approval of this

product in treatment-naive patients. And as the presentations have focused on renal safety as a primary concern, we would like to have your input on the best approach to monitoring both the frequency and the types of tests that should be conducted.

Finally, although we've had a little bit of this discussion already now, any discussion of postmarketing studies that you think might be needed to flesh out either the safety profile or efficacy in the population as a whole or in specific subgroups. Thanks.

Questions to the Committee and Discussion

DR. MURATA: Thank you, Dr. Lewis.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So I will read out Question 1 and open it for discussion. Question 1, please comment on the

safety profile of E/C/F/T, as abbreviated by the FDA, focusing on the proximal tubulopathy and the other renal adverse events leading to subject discontinuation.

This is now open for discussion, so Dr. Hunsicker.

DR. HUNSICKER: I'm going to continue my little disquisition on the impact of the tubular things. What I talked about in response earlier to Dr. Wood was what was the impact of incomplete return of the creatinine to normal, and I'm not going to go back over that.

But I want to point out a couple of things about the tubulopathy. First of all, the only -- it is not true that reduction of renal filtration is the only possible adverse effect associated with the tubulopathy. And in particular, the things that are typically associated, as you've heard this morning or this afternoon, about the tubulopathy, are phosphate wasting and impairment of vitamin D metabolism and a few other things. Also, there is a tendency to acidosis, a so-called renal tubular

acidosis associated with the Fanconi, whether it's overt or otherwise.

The major adverse effects associated with these tubular changes are probably going to be expressed in the bone. So that I think that when you're looking at the potential for adverse effects, you should focus not just on the possibility of ultimate renal insufficiency but also the bone effects of this drug.

Now, I personally think that the signal that we have from the studies is pretty good, but I think that it would require a fair amount of attention.

The second thing perhaps along the same line that I want to comment that picks up something that Dr. Wood said is that it almost certainly is the case that there are different people who are going to handle this drug differently depending upon genetic or other possible but particularly genetic things. And I should think that the sponsor or somebody else should be looking to see why it is that some people develop this tubulopathy and

others don't. It's not going to be just a random event. There's some cause for it.

The third thing that I want to talk about really picks up something that Dr. Estrella said earlier on, which is that the earlier that you can detect this tubulopathy, the more likely it is that you're going to be able to discontinue the drug soon enough to avoid any real permanent damage.

There is one potential sort of un-nice thing about this situation which is well known to us in nephrology, which is that drugs which adversely affect the kidney are frequently also excreted by the kidney. And as I understand it, tenofovir is largely cleared by the kidneys so that as you lose your renal function, you will then actually have an increasing exposure.

This puts a real emphasis on the need for early detection of an abnormality, and I'm not sure, as I said yesterday, that the -- looking at creatinine or dipstick proteinuria, which looks like for albuminuria, is the best way to do this. Now, I don't necessarily have a clear suggestion

here, but I think that there is a real need not just for this drug but for the whole thing that includes Truvada and the evidence for and evolving evidence for tubulopathy for study of the early detection of renal damage in people who are on this drug, whether it's part of QUAD or part of any of the other things.

I just want to emphasize that before we go on. I don't think that it is a QUAD issue specifically, although there may be a separate QUAD issue. But I think it is an issue that has to be addressed in terms of the long-term safety of anything that contains this particular combination of drugs.

DR. MURATA: Thank you.

Dr. Wood.

DR. WOOD: I just came up with another question that maybe Dr. Cheng can address for me. The 11 patients who discontinued, do we have a list of the concomitant medications that they were on? I know that one of those 11 was on acyclovir, but do we have any sense of what the concomitant

medications were of those 11 patients and whether or not there were any commonalities among that? That's the first thing.

And then the second question, again, goes to our nephrology experts. I don't know out of commonly prescribed medications, drugs that are known as kind of like the number one offenders for proximal tubulopathies and whether or not those drugs are likely to be co-prescribed for this patient population.

So that's my general question. Are there top known offenders in terms of proximal tubulopathy drugs, and are patients with HIV infection who are likely to be receiving this also likely to be prescribed those drugs?

DR. MURATA: Perhaps I would ask first the sponsor, if available, to address Dr. Wood's first question, and then we'll go to the renal consultants.

DR. CHENG: In terms of the commonalities of con-meds between them, besides acyclovir, there was one patient who was on low dose non-steroidals.

But at this moment, I don't have all the con-meds for all the patients, all 11. We were primarily focused on the nine that were on the COBI and elvitegravir; the other two on atazanavir and ritonavir.

DR. WOOD: I think it would be very critical to examine specifically non-steroidal use because those are over-the-counter classes of agents that we know clearly can adversely affect renal function. And if there's some commonality there in terms of common use of those, I think it would be important to know.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: There are some drugs that are associated with tubular toxicity, namely, antibiotics, but those are generally given in the inpatient setting such as amphotericin and gentamicin, those sorts of things in which we practitioners, physicians generally, monitor the patients closely for nephrotoxicity.

Most commonly, I think drugs that predispose to nephrotoxicity and other exposures are generally

more in terms of NSAIDS, et cetera, would be of greater concern in which a decline in GFR could lead to accumulation of tenofovir.

DR. MURATA: Thank you.

Dr. Strader.

DR. STRADER: On that same point, I'd like to ask our renal colleagues to then define how you would go about testing a patient to see early on whether or not they have proximal tubulopathy. You've already suggested that somehow creatinine is not good enough to use, and certainly, that a urine dipstick is not good.

What kinds of things do you suggest we do or recommend be done to identify these patients early on?

DR. HUNSICKER: Do you want to try that one?

DR. ESTRELLA: Sure. So our practice at this point is -- unfortunately, cystatin C is not clinically available at all centers, so we are -- in terms of kidney function, we're limited to serum creatinine at the moment. In terms of tubular toxicity, urinalysis and in patients who already

have baseline proteinuria, I'd recommend at least having quantified proteinuria to have as a baseline to follow. And in those who develop incident proteinuria on drug, again, quantification of proteinuria would be helpful.

DR. HUNSICKER: I'm going to demur very slightly with respect to cystatin. I have to tell you, I'm not a great admirer of cystatin, but I think that cystatin is now widely available. It's available in almost every hospital as a mail-out, and I think that if there is any question about the significance of a change in GFR in response to the effect of TDE (ph) or whatever the hell the blocker is there -- I got my names confused here now.

But if there's any question, it should be, I think, part of the labeling that there are alternative ways of assessing GFR, either by radionuclides or by cystatin. That it should not be left to the prescribing physician. It should not be left in a quandary as to what to do when there is an elevated serum creatinine. There are ways of resolving this.

With respect to the broader question, I think this is a research question that needs to be addressed by somebody. I told you yesterday that often what happens when you get tubulopathy is you get a batch or changes before you get any real change in your GFR. And particularly if your GFR starts normal, you have to have a fairly big change in the GFR before you can detect it anyway.

But there are all sorts of changes that are happening. Now, the sponsor has given you some information about phosphate levels, serum phosphate, or the fractional excretion of phosphorous. They've given you some discussion about glycosuria.

I mentioned yesterday that the proteinuria that you get that is a result of non-reabsorption -- we believe, of non-reabsorption of filtered proteins and tubular proteins is disproportionately low molecular weight protein in the case of tubular dysfunction. And so looking for protein -- for albuminuria, which is what you test with a dipstick, may be quick insensitive to

that. You can look for total protein in the urine by nephelometric. That's the standard way. You add some precipitating agent and look at how much turbidity is. That, you can do.

You can also look for specific proteins that are more frequently excreted in the urine in patients with tubular injury, beta 2 microglobulin is one of them. The other one is NGAL is one of the things.

I think that there is an issue here of finding out what is the best way to detect a tubulopathy early so that the drug can be stopped, sparing the acceleration that you get when you get decreased GFR and then suddenly, you're getting increased tenofovir exposure, more injury, more exposure and so forth.

You've got to get in early, and you've got to establish a way to do that testing on a repeated basis so that you can stop the drug when you first see evidence of tubular injury.

DR. STRADER: That's what I'm asking you. You don't know what those tests would be?

DR. HUNSICKER: If I knew what the right answer was, I would have said it much more quickly than I did.

(Laughter.)

DR. MURATA: Okay. Dr. Daskalakis.

DR. DASKALAKIS: So very specifically addressing or making comment on discussion point 1, I think that we're seeing a very small length of time, a very short study, that there may be a signal for renal toxicity that is way more complex than what the average provider is used to dealing with.

So I feel that if you were to sort of look at the safety profile, the answer really looking at the labeling if this were to sort of go on for approval, you'd need very, very clear guidelines for providers as to starts and stops. Just like you have very clear guidelines for when to do a dose reduction, a fixed-dose combination with such complex renal toxicity, I think, would need a very clear statement on the label of if this, then that. And if then this, then do this, because I really

feel like we have a very small experience and have to compensate with a lot of guidance.

DR. HUNSICKER: May I have the right to say one thing back? We have one good thing on our side with respect to this. Unlike yesterday, we are not really trying to announce this to every general practitioner in the country.

There is a limited group of people that take care of HIV patients, and surely, people who are on this for treatment should be under the care of an HIV expert. And I think it will be much easier to get that community up to snuff on how to deal with this issue than it would be what we were talking about yesterday.

DR. DASKALAKIS: So I'm going to just respond to that, too. I do agree with that. I really think that this drug is a very simple once-a-day regimen that requires a pretty high level of management. But sort of looking at the Atripla story, I feel that with a drug that is so simple to write and administer without a lot of adjustments necessary, that there may be some folks

who will become more comfortable with using this as a first line in naive patients.

Sort of just like Atripla is prescribed by more and more non-HIV specialists in general practice, I agree with you, and I echo that even more so. We just sort of need to be prepared for an easy drug that patients like and that will have good marketing, to be something that general folks that are not HIV specialists are going to give. And so the guidelines, I think, need to be very clear as to what to do and what the testing patterns should be for supervision.

DR. MURATA: Okay. And Dr. Cheever.

DR. CHEEVER: This is also for our renal colleagues. So we did see that early on we had some signals that some of these patients were going to have problems. But do we know what the average course is of tubulopathy? Because I'm thinking some of these patients, once they're stable, we're seeing them every three to six months. And I must say, for my patient population, I do order labs. Whether or not they do their labs is a whole other

question even though they'd be done in the clinic based on a variety of things, including whether or not they feel they can urinate in the time that they're in with us and then they don't come back again for six months.

So we do sort of not -- even though we might order labs regularly, we don't always get them in this general patient population. So if I'm ordering labs every -- do I order labs every three months, every six months in terms of urine -- like what is the signal between first seeing the signal and running into a lot of problems?

DR. HUNSICKER: I think today with what we know today, the criteria that have been laid out by the company are probably a good starting point. What I'm suggesting is that we can probably do better. I think that's my shorter way of saying that we don't know yet, but we ought to know.

It looks -- you've seen what the results were. It does not appear that this is something that only appears in the first two weeks. It would be really nice if you could say that all of the

episodes were in the first couple of weeks, and after you've watched that, you're not in trouble. Unfortunately, that's not what happened. They were later on.

Now, how clean are these? Gosh only knows, as my colleague here who is an expert in AIDS nephropathy, or at least has studied AIDS nephropathy more than I have, we've got a messy situation here. These people have many more than one thing wrong with their kidney, and you're trying to see the impact of your drug in the middle of all that.

I think that what we have is adequate to start with, but I would just urge the company to find ways of detecting this earlier, taking into account that we're not dealing with a glomerularopathy. We're dealing with a tubulopathy.

DR. MURATA: Dr. Ellenberg.

DR. ELLENBERG: I wonder if we could just sort of take several steps back, and I have a question for my colleagues who do treat

HIV-infected subjects to help me understand about this issue. So what sorts of patients would you -- if this were available, who would you choose to treat with this as compared to other once-a-day FTC agents?

DR. MURATA: Any response, Dr. Daskalakis?

DR. DASKALAKIS: So I would -- Demetre Daskalakis -- one population that I would think about are folks who cannot take Atripla or efavirenz for some reason. So specifically, if people have some psychiatric overlay potentially, and also, if there are people who are working specific shift kind of work.

I'll also say that since the guidelines do give an option as a first line for folks on raltegravir and Truvada, though there aren't studies yet, I think there will be some providers who'd have a tendency to consider switching BID raltegravir and once-a-day Truvada to a once-a-day QUAD pill since this is probably equivalent from the perspective of resistance.

So I think that those are probably the top

folks that I would think about. I think there would still be a lot of folks going on Atripla, but I imagine if this is approved for naive indication, that a once-a-day pill, depending on people's lifestyle, that doesn't have neuropsychiatric side effects to the same level may make it pretty appealing.

DR. ELLENBERG: So this could be a first choice. It wouldn't just be for people who didn't like the side effects that they got from one of the other treatments to move to this. There would be people who would actually be started with this as their first.

DR. DASKALAKIS: I think so, yes. I think that people -- I don't want to be the only voice in this, but I feel like people would pick the QUAD as a first line regimen in naive, in folks never previously exposed to ARV.

DR. MURATA: Dr. Giordano, do you have a comment?

DR. GIORDANO: I just concur completely with Dr. Daskalakis' comments.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: I just wanted to comment, I guess, on discussion point 1. I think overall in the results that we've seen today that we see that the rates of renal toxicity are pretty low, but we know from the previous studies related to tenofovir that we have different observations when it comes to sort of population-based studies.

So I think to fully assess the safety profile of tenofovir, I would feel more comfortable with seeing sort of the longer outcomes as the results we've seen today are mainly at the 48-week cutoff and the studies are ongoing.

Also, I had concerns in terms of the lower representation of women, and we know that tenofovir toxicity tends to be more common in those with low body mass, which most women are, and also, low representation of individuals with chronic kidney disease or risk factors thereof. So I think there are still sort of ongoing questions with regards to the safety profile.

With the questions in terms of detecting

tubulopathy, there have been several small studies looking at different things such as NGAL, retinol binding protein, but all of those are not readily available to the common practitioner who would be prescribing tenofovir-based regimens at the moment.

The other caveat with regards to GFR estimations in the context of HIV infection, most of the studies -- similar to the general population, most of the studies looking at GFR -- and Dr. Hunsicker can actually speak on this a little bit better probably than I can -- used mainly individuals with impaired kidney function. And so those GFR equations do much better when your GFR is already less than 60.

So individuals with an estimated GFR above 60, those could range anywhere from 60 to 120, and the reliability and accuracy of those estimations may be misleading.

DR. HUNSICKER: Let me speak to that since you've invited me to speak to it. There are two serum creatinine-based estimates -- well, three actually -- the one that estimates the creatinine

clearance, which is the Cockcroft-Gault, which is essentially of historic interest primarily.

There's the MDRD equation, dear to my heart, since I was one of the PIs of the MDRD study, which has the great disadvantage that it actually misestimates the GFRs in the range that Dr Estrella was just referring to. And then there is the CKD-EPI.

The CKD-EPI is the formula that should be used. It is the least biased in the normal range or the high, towards normal range, which is the area that we're really interested in looking at here. I would rush to say that its precision with relation to true GFR is not exactly linear and neat, but it is better than anything else. And so probably you ought to be recommending the use of the CKD-EPI.

There is an evolving thing in laboratories right now. Up until recently, typically, GFRs based on serum creatinine were reported as either above 60, as you've just heard, or abnormal. With the introduction of the CKD-EPI formula, which is

now more unbiased all the way up to around 120, many laboratories are now moving back towards giving you a real numeric estimate of the GFR based on the whole range of creatinines. And I think that that will make things easier.

It doesn't help the clinician very much to say that if there is a 20 percent drop in the GFR, you should do something about it when that 20 percent drop is from 90 to 70 and all you get is better than 60. And so we've got a problem here. But this isn't the AIDS community problem. This is the whole community's problem of understanding how to interpret GFR estimates in terms of creatinine levels. But you should be using CKD-EPI, which is I think what Dr. Estrella was trying to tell you.

DR. ESTRELLA: With the caveat that it hasn't been well validated in HIV-infected individuals.

DR. HUNSICKER: That's correct.

DR. MURATA: Dr. Giordano.

DR. GIORDANO: This isn't related to the renal issue at all. I know that the indication

that's being sought is in naive populations, but one issue that I think needs some attention in future studies for safety -- so it's sort of between a few of these questions here, but related to the safety issue -- is what does happen if you were to administer this drug with a PI concomitant.

Because I see one niche for this drug as you've got someone who has failed an Atripla fixed-dose combination and now has a 184, and they either -- and they perhaps didn't tolerate the efavirenz component or, in fact, had virologic failure. And they've got a 184; whether they've got a K103 or not is irrelevant, but they've got some resistance to -- potentially some resistance to Truvada at least in the genotype.

Now you're saying what's the next regimen going to be for this person, so they should be integrase inhibitor sensitive, and this would be a great drug. But you maybe would want to add an additional drug on there because they might have some resistance to the FTC component.

So I could easily see clinicians saying,

well, let me just -- you've already got the booster onboard. Let me just throw on some darunavir or throw on some atazanavir. So knowing what would happen in a drug-drug interaction study would be very helpful in that scenario.

Is that planned? Is that something that is underway?

DR. MURATA: Can the sponsor respond, if any?

DR. KEARNEY: That's a very good question. We did that experiment. We gave COBI with elvitegravir and darunavir. Unfortunately, the COBI levels go down, the darunavir levels go down, and the EVG levels go down. So that option is not viable currently.

That is why the indication is stated and it's recommend to be a complete regimen and not to be used with other antiretrovirals. We do have some ideas to study this area a bit more.

DR. GIORDANO: Is that information public, that the drug interactions prohibit use of darunavir with this drug?

DR. KEARNEY: Yes.

DR. HUNSICKER: That actually has to be in your labeling information, and you have to make sure that people get informed about it because I'm concerned about the same thing. Somebody is going to say, well, I'll just add this up. That cancels out what you're doing. Don't do that. They've got to know this.

DR. MURATA: Any other comments on Question 1 discussion? Yes, Dr. Ellenberg.

DR. ELLENBERG: Is there anything else we haven't asked about that would be good to know?

(Laughter.}

DR. LEWIS: We're not hiding anything.

(Laughter.)

DR. MURATA: Mr. Raymond.

MR. RAYMOND: It just brings to mind also the question of concomitant use with future hepatitis C treatment regimens. We talked about the drug-drug interaction potential with COBI, but it also makes me wonder about ribavirin as well, which is likely to remain part of at least some of

the regimens, even without interferon, as I'm sure the sponsor are well aware of.

So I'm not clear on what would be useful just because of the overlap between hepatitis C, kidney issues and stuff like that. I wonder if there's something there to be looked at or concerned about.

DR. MURATA: It looks like some of your questions -- some of the points that you had asked are relevant to later discussion points.

Does the agency want the sponsor to comment on this or defer till later? Perhaps if you're on the topic of -- and to facilitate the discussion, there appears to be many postmarketing studies planned or in the works that have direct or indirect relevance to actually the discussion points.

So as the chair's prerogative, it may be helpful for the entire panel if the sponsor can provide an overview slide or two of the ongoing and the planned studies; perhaps jumping the gun to point 4, but again, in the context of the safety

issues.

DR. CHENG: So we've already touched on a number of the ongoing clinical studies that are going, but if I understand Mr. Raymond's question appropriately, he has specific questions about drug-drug interactions that relate to HCV protease inhibitors and potentially ribavirin.

I'll ask Dr. Kearney to speak to that in terms of the upcoming clinical pharmacology studies that we have planned or are in the works already.

DR. KEARNEY: This project is a pharmacologist's dream, right?

(Laughter.)

DR. KEARNEY: So I touched on a bit earlier the studies that we're now designing with the HCV PIs as well as a number of HCV compounds that we're developing, and we've done some collaborative studies within our HCV collaborations with other companies. And we're now starting to loop that into the HIV program here.

The ribavirin question is an interesting question because of its long half-life and

teratogenicity. It's a challenge in terms of doing these studies in healthy subjects. We have done some exploration in that area.

In some studies, also looking at literature reviews, you also don't see -- ribavirin has very rarely been implicated in a pharmacokinetic drug interaction. And so I think once you establish some degree of comfort and understanding of the PK of your drug in combination with ribavirin, you can kind of look at historical data as well and move around.

As it relates to some specific drug interaction studies we're planning on doing for this program, things we're interested in looking at is to address this question of the double boosted regimen. That's kind of the jargon that we use. Could you use more COBI with the ritonavir and elvitegravir?

We have a collaboration with Tibotec to co-formulate darunavir with COBI. And so we're interested in looking at a drug interaction study that we could possibly give QUAD plus this duo of

COBI darunavir. So you'd basically double the dose of COBI, and then we want to assess that pharmacokinetically first as a way to potentially address this question.

Other things as it relates to some of the restrictions we're proposing in labeling in terms of moderate inducers, carbamazepine being an example, we're planning on doing a drug interaction study with that to understand whether the threshold needs to be moderate inducers or more strong inducers, which we know will stay.

So those are the ones that we've already got on the books and are planning to do, but they're always evolving.

DR. STRADER: Doris Strader. So you are planning to do studies on HIV HCV co-infected patients who are taking QUAD and a protease inhibitor for their hepatitis C or yes or no?

DR. KEARNEY: We are planning on doing a healthy subject kinetic study first to make sure there's not some wild swings in PK, and then that would inform co-infection studies that we may be

able to do.

DR. STRADER: Okay. Thank you.

DR. MURATA: Thank you.

Dr. Wood.

DR. WOOD: Lauren Wood. Going back to our nephrology colleagues again, can you comment? The renal dysfunction that's associated with chronic NSAID use, I don't know what the nature of that is. I'd like you to, one, comment on that.

And since we don't know yet about the concomitant NSAID use in our safety cohort, my next question to you is, since all of the renal safety data is fairly early on, median of 60 weeks in the cohort, we don't have a lot of long-term data, and out of the 11 individuals that had discontinuation for renal issues, all of them still have abnormal creatinines.

Do you think that -- should there be some kind of labeling precaution about nonsteroidal use on the label with this drug since we just don't know?

DR. HUNSICKER: Let me give this one a try.

We are treating human beings. Human beings have pain. If we say that they can't take NSAIDs, they'll wind up taking narcotics. Is that better?

I think what we have to do is to recognize that the NSAID use -- first of all, back up. How does NSAIDs affect your renal function? It does two things. First of all, in everybody, it reduces the GFR. It reduces the GFR because of what it does to the afferent and efferent arterioles.

In a subset of people, it causes interstitial nephritis, which is an adverse effect; it's a sporadic adverse effect. It's predictable that if you take one of these agents that you will reduce the GFR. You will therefore increase your exposure to anything that is cleared by the kidney. This is well known to most people, I would think, in internal medicine that you have to be very careful about the use of NSAIDs in people that have diabetes, hypertension, whatever it is because it makes a lot of those things worse.

I think to say that you cannot use NSAIDs is just utterly unrealistic.

DR. WOOD: I wasn't suggesting that we say that you can't use NSAIDs at all. I guess one of my real concerns is something that would heighten the awareness where if you know that your patient is chronically taking NSAIDs and you are going to prescribe them the QUAD pill, just what kind of threshold would you have?

I mean, if you knew that -- let's just say you were also going to be treating patients with HIV. If someone came and they were going to have one of the approved indications that Dr. Daskalakis mentioned in terms of you're going to consider starting them on the QUAD, is there some kind of threshold that if you knew that your patient took non-steroidals every day because they've got chronic arthritis, would you continue -- would you go ahead and prescribe the QUAD?

That's what I'm trying to get at. I'm not trying to say that we have some kind of formal labeling indication that says you can't take non-steroidal. That's not realistic. I agree. But based on the data that you've seen, would there

be some kind of threshold where if you knew that your patient was taking Aleve twice a day and they took it all the time, would you put them on the QUAD pill?

DR. HUNSICKER: Let me answer that by saying that there's an analogy here to the major issue in internal medicine of drug dosing in elderly people. Now, I'm elderly, I know, but I'm not talking about that.

GFR goes down with age. If you use drugs the same way in old people that you use them in young people, you're going to get more renal toxicity. That's just clear. We know that. Well, I won't say we know that. I know that, and a lot of people know that. Unfortunately, we see misuse of drugs in elderly people all the time.

I think this is of the same variety here. Some components of QUAD are renally cleared. Clearly, as the GFR is adversely affected, you're going to have more trouble with it. That's why the sponsor says when the GFR gets below 50, you can't dose the stuff because you've got four fixed pieces

that don't behave the same.

I think you just have to say that in the presence of things that adversely affect renal function, that you're going to have to be much more careful in use of this agent.

DR. ESTRELLA: I have nothing to add.

DR. MURATA: Any other comments, questions regarding this discussion point? Yes, Dr. Strader.

DR. STRADER: Based on what you just said then, would it be reasonable to say if your HIV positive patient you're considering to treat with this drug has diabetes and/or hypertension, they should have their GFR tested by this CKD-EPI test that you recommended earlier and that this should be done on a regular basis rather than just measuring creatinine in these individuals because they're more likely to have issues in the future?

DR. HUNSICKER: I don't know I got all of the details of your question, but yes, as the patient is having more and more things that threaten renal function, you have to be more and more careful about the use of a drug that is

cleared by the kidney.

DR. ESTRELLA: I think the most recent guidelines in terms of renal function assessment in individuals who are HIV infected already recommend regular renal function monitoring if they have known risk factors for kidney disease, such as diabetes or hypertension or family history of kidney disease, also.

DR. STRADER: That I understand. What I'm trying to get to is what do I recommend that they test or do. It's very vague, renal function should be monitored. So with what test should we do it?

DR. ESTRELLA: The CKD-EPI equation is based on serum creatinine.

DR. HUNSICKER: Let me just clarify one thing. I'm not -- all of what I've said about renal function is not specific to QUAD. It's generic to anything that has the Truvada combination in it.

DR. MURATA: Dr. Giordano.

DR. GIORDANO: If I may comment, the good news is this has tenofovir in it. And every HIV

prescriber knows that you be careful when you've got any renal potential when you prescribe tenofovir in anyone who's got potential for renal adverse events. So this isn't going to be new to anyone who's doing on any kind of routine basis.

The fact is that maybe there's an increased risk because of the cobicistat, and I think that will not go unnoticed. But I don't see a major problem with having to do provider education around this issue because we're already very aware that tenofovir has renal issues.

So I'm not too concerned that the providers are going to miss something here. They need to maybe raise the bar a little bit higher, maybe have a little bit higher index of suspicion, but I don't see a major change necessary.

DR. MURATA: Dr. Daskalakis.

DR. DASKALAKIS: So I guess reflecting on that as well, I think you're right for sure that tenofovir is going to be sort of the tracker, the tracer in the drug that will keep you sort of honest with your creatinine checks.

But it seems as if we've also had this conversation about using glycosuria, proteinuria, and potentially phosphate to sort of make some decisions about the drug. And so we haven't really talked about should that be something that's sort of clearly in the label as well. So if you have a certain amount of hypophosphatemia, if you have glycosuria with a normal serum glucose, these should all be things that should make you stop the drug or just increase your concern?

From the real perspective, what do you guys think?

DR. HUNSICKER: The adverse effect of tubulopathy, short of what it does to GFR, is likely to be expressed in bones. And so I don't see a big problem with bones. I don't see a huge number of fractures. Remember, we're talking about tenofovir which is in everything. I suppose you could ask would you rather have a little bit of bone loss or die of AIDS. To me, it's not a very difficult question to answer.

DR. ESTRELLA: Based on clinical experience,

I would be more conservative in that individuals who have clear proximal tubular toxicity should probably be discontinued off of tenofovir-based regimen.

DR. DASKALAKIS: Were you able to give -- I mean, are there clear guidelines as to how you would define early proximal tubulopathy based on the testing that we're able to do?

DR. ESTRELLA: I think that is what you'd mentioned before, normoglycemic glycosuria, proteinuria, metabolic acidosis, hypokalemia.

DR. HUNSICKER: So I would say that you use all of these other testings as a way of saying watch out, you may be getting into trouble. Now, when you have overt evidences of a Fanconi, which we have seen associated with rises in GFR, then I think it's time to find an alternative regimen. But I wouldn't stop just because you have a low phosphorous one time. I wouldn't stop just because you've got a little bit of glycosuria, and a group of patients may well I have diabetes. But you should be certainly triggered to look into what the

heck is going on and know that tubulopathy is a problem.

DR. MURATA: Dr. Cheever.

DR. CHEEVER: So I agree with Dr. Giordano in the sense that most of us that use tenofovir regularly have run into problems with at least one patient somewhere along the way, the diabetic patient that was doing fine till she had gastroenteritis and became severely dehydrated. We've all had those bad experiences, I think, somewhere. So I think that's true.

My concern is that with the -- in this case where you're supposed to see a little bump in your creatinine because you're not excreting it normally, that you sort of chalk that up to, oh, we're supposed to see that. And I do think that it would be helpful in terms of some education to providers to really think about is that creatinine just what you're expecting to see or is -- do you need to worry about tubulopathy here and what should I do next?

Because I regularly get urine proteins on

patients who are on tenofovir, but if they had a little bit glucose in their urine, I'm not sure if I would -- obviously, you're not supposed to be there, but a little bit of glucose, whatever, on to the next thing. And just so they can really note those things.

The other thing I had thought about to be mentioned is the fractional excretion of phosphorous is something that we sometimes calculate, and I'm just -- if you can't be doing that with this drug which is changing around your excretion of creatinine, then maybe a little education about that as well would be worthwhile to people.

DR. HUNSICKER: Well, on the tubular excretion of phosphorous, I've seen what you've got up there, if it goes from 5 percent to 8 percent, I don't care. If it goes from 5 percent to 35 percent, you're in trouble. I mean, there are quantitative changes.

Now, I suppose because I'm a nephrologist, you could always refer them to one of my partners.

However, I will tell you that the average nephrologist --

DR. CHEEVER: It's a four-month wait in my institution to see a nephrologist.

DR. HUNSICKER: The average nephrologist doesn't know any more about this than the average general internist because they're all dealing with patients on dialysis, and patients on dialysis tend to have phosphorous go in the other direction.

I think this is something that just needs to be part of the educational process. That's all.

DR. MURATA: Yes, Dr. Wood.

DR. WOOD: Your comment that the renal tubulopathy is likely to be manifested in the bones, so the question I know have for the sponsor is out of those 11 patients who had discontinuation for renal events, do you have any idea what their BMDs were compared to the rest of the individuals who were not taken off for renal adverse events? Was there a major difference in them? Because it was done at week 48, right, was when the repeat BMD was done compared to baseline?

DR. CHENG: No. There was BMD done at week 24 and week 48. There was only BMD done in Study 103. There were no renal discontinuations that met proximal tubulopathy in Study 103. All the QUAD patients came from Study 102 for which there's no BMD monitoring.

DR. WOOD: Oh, okay.

DR. HUNSICKER: I am obliged to say that this is a two-year study, and you don't know what's going to happen after more years if there is a constant phosphate leak. And so we can't just brush it off that way, but we don't have data on it today.

DR. MURATA: So it may be a reasonable time to summarize the ongoing discussion that we've had for some time now. With regard to this question, numerous points, especially with the help of our renal colleagues, primarily, there were classifications, review of tubulopathy, issues about different patients responding differently to this combination, drug population-based pharmacogenomic responses.

The key -- some of the recurring themes in the discussion appear to be the following. First, the perceived and the practical need to monitor for renal toxicity and how to do it and which available tests. And there was an extensive discussion about that. I guess the tendency amongst the panelists was earlier detection of renal abnormality is probably better than later.

But in terms of specific renal tests in the parameters of clinicians who routinely see HIV patients or in the nephrology world, urine, protein glucose, creatinine urinalysis, urine dipsticks, those issues were discussed.

As far as actual measurements of kidney function, three methods including the CKD-EPI was mentioned, probably the least biased but probably the least used, if I understand correctly, among the HIV population at the moment.

Then there were points that were raised in the discussion that are probably relevant in this context of Question 1 as well as to the later discussion points, including how the lower number

of females that were enrolled. That may play a role because of low body mass and the renal impairment in that context and lower enrollment of patients with chronic kidney disease.

There were several drug-drug interactions that came indirectly discussed, and we can go through in detail later. But some of the mentions were anti-seizure medications, anti-HCV, antiviral such as ribavirin.

Lastly, our renal colleagues and others have cautioned about the data that had been discussed so far in terms of limitations of a two-year study, so.

So that's the chair's summary of the main discussion points of Question 1.

Now, the Question 2, would the agency wish to proceed with Question 2?

DR. BIRNKRANT: Yes, please.

DR. MURATA: Let me read the question first and then open it for discussion and then after the discussion, if any, are done, then I will read the requisite comments about the voting procedure.

So Question 2 is for a vote by the panel. Considering the overall risks and benefits, do the available data support approval of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as a complete regimen for treatment of HIV-infected treatment-naive adults? If no, what studies are recommended? If yes, proceed with the remaining questions as for discussion.

So now I will open for any discussion for the question to be voted here.

Mr. Raymond.

MR. RAYMOND: I'll just say I do think that we've got enough information to make this decision. It looks like very good efficacy data even with the limitations of -- unfortunately, a kind of narrow funnel in terms of the current study population. Even with the renal issues that have been identified, I think that while they're not completely easily predicted, and there's questions about detection that we can address in the later questions, that this will be useful addition to the

HIV therapies that we have.

DR. MURATA: Let me correct one minor administrative portion on my part. I do need to read this prior to further discussion.

We'll be using electronic voting system for this meeting. Once you begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until questions have been answered or discussed.

So again, this is more of administrative reading on my part, and then we can proceed with the discussion for voting question.

Mr. Raymond, have you completed your statement or?

MR. RAYMOND: Yes.

DR. MURATA: Now we're ready to vote. We will begin the voting process if there are no further discussions. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again.

(Vote taken.)

DR. WAPLES: For the record, 13 yes; one no; zero abstain.

DR. MURATA: So we will go around the room, if we may start with Dr. Estrella.

DR. ESTRELLA: Hi, I was the lone no vote. My main concern in terms of -- that led me to vote

no was that there -- I think at this point in time, there are plenty of alternatives to QUAD in terms of treatment of ART-naive individuals, and I think there were enough questions with regards to ongoing studies in terms of safety profile that led me to my decision, mainly that most of the data reporting on the safety profile were within the 48 weeks of follow-up when most of the renal toxicities that we saw were beyond those 48 weeks.

I think that is mainly what led me to my decision for no, and also with regards to lower representation of women and individuals at risk for CKD. And I didn't feel like there was really no huge hurry in approving this drug until the outstanding studies were completed.

DR. WAPLES: I'm sorry. I apologize if you already said it, but can you say your name into the record?

DR. ESTRELLA: Michelle Estrella.

DR. HUNSICKER: Larry Hunsicker, I voted yes. I believe that the evidence for efficacy is very strong. I think that the toxicities are

largely related to the components of Truvada, which is part of everybody -- not everybody but most people's regimen anyway. And the incremental thing that's associated with the adding of COBI and the other thing have not been proved to be very substantial. So I think that it is safe.

I do agree that there are alternatives, but that's not what we are called to judge. I believe it is safe and effective. I do agree that we do need to do further studies, which we'll talk about later.

DR. VEGA: Hi. Marlena Vega. I voted yes. On the heels of a lot of the points, but particularly the efficacy, I think you met the standards. And also, I'm still feeling good about all the answers I got for my question before.

DR. WOOD: Lauren Wood. I voted yes because I think the demonstration of efficacy was clear.

DR. GIORDANO: Tom Giordano. I voted yes. I think that the data clearly indicate that this is a safe and effective drug.

DR. MURATA: I'm Yoshi Murata. I voted yes

for the reasons as discussed by Dr. Giordano.

DR. STRADER: Doris Strader. I voted yes. I think that the data showed that this drug was non-inferior to those with which it was -- against which it was tested.

DR. GLEN: Jeffrey Glen. I voted yes. I thought this was a more convenient combo containing a new mechanism of action component with demonstrated efficacy whose major toxicities appear to involve a possible increase of a known toxicity associated with tenofovir and identifiable drug-drug interaction toxicities.

DR. DASKALAKIS: Demetre Daskalakis. I also voted yes for this new efficacious combination that has a positive risk/benefit ration.

MR. RAYMOND: Daniel Raymond. I voted yes for reasons already stated.

DR. ELLENBERG: Susan Ellenberg. I voted yes because the efficacy seems clear, and the safety issues that have arisen while real seem to be quite manageable.

DR. CORBETT: Amanda Corbett. I voted yes

for similar reasons on efficacy and will be very interested to see future interesting pharmacology studies.

DR. KUHAR: David Kuhar. I also voted yes because I think safety and efficacy were demonstrated.

DR. CHEEVER: Laura Cheever. I voted yes for the reasons already stated. I was concerned about the lack of women in the study. It looks like that's being addressed.

DR. MURATA: Okay. So the votes were as just shown. The points as a summary of the comments, essentially, the panel members who voted yes mentioned points such as favorable risk/benefit profile, the demonstration of efficacy as for the requirement of the registrational studies. And then the safety profile issue was discussed by panel members regarding its management, whether it's favorably managed or requiring additional studies.

So now we move on to Question 3 for 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. Let me just read all three just for completeness, and perhaps we can start with the first one. 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?

Point B for discussion, 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?

And 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.

So perhaps we can open up point A for discussion. Dr. Hunsicker.

DR. HUNSICKER: First, one thing that I do want to have the further study of is the question of either the pharmacokinetic or pharmacodynamic interaction between COBI and tenofovir. I make this comment based on the observation that the renal toxicity seemed to be higher in the QUAD but also in the drug treatments that included ritonavir.

There is a suggestion that actually the ritonavir or any of these enhancers are not absolutely irrelevant to the tenofovir. And since tenofovir is the thing that seems to be associated with most of the toxicities, I think we need to understand that better.

Answering the three questions, that's very simple for me. A, would additional laboratory monitoring be useful, to be determined? I think it needs to be studied. I think in the interim what you've got is adequate.

Would renal safety be enhanced by monitoring

renal function in all patients? Yes, of course.

(Laughter.)

DR. HUNSICKER: Should laboratory cutoffs be provided to help distinguish the effect of cobicistat on serum creatinine as opposed from genuine renal dysfunction?

I think that the distinction is made more easily if you look at alternatives of ways of estimating GFR, and I think that probably that there should be information about the use of cystatin or other ways of getting at this in the books.

I do understand and I take from Dr. Estrella that we have to be aware of the fact that some of these tests may not be available in all parts of the world. But I think that at least the managing doctor needs to know that it isn't necessary to stay ignorant about what's really going on. There are measures that distinguish these things. But in the meantime, I suspect that the sponsor's .4 milligram per deciliter is as good as any other one and probably adequate.

DR. MURATA: Dr. Estrella.

DR. ESTRELLA: I guess to go down through the list, in terms of A, I think we've discussed that in terms of urine dipsticks and serum creatinine or what is clinically available currently.

In terms of in patients with baseline glycosuria or proteinuria, I think it would be difficult to find another measure or a substitute for glycosuria outside of the ones that are currently under study that have been mentioned before.

But in terms of proteinuria, I think this is where protein quantification, either by spot urine protein to creatinine ratio, would be of help.

To answer B, yes, and there has been, as mentioned yesterday, a study of about 10,000 individuals within the VA HIV cohort which showed basically no differences in terms of risk for tenofovir in individuals with or without risk factors for kidney disease at baseline. And so how I interpreted that was basically all individuals on

tenofovir are at risk for toxicity regardless of their baseline traditional risk factors or not.

In terms of the cutoffs that were provided by the sponsor, I think the only thing I may add would be basically a different parameter other than an absolute -- in addition to the absolute increase of 4 milligrams per deciliter, some sort of percent increase in serum creatinine.

Just as an example, if someone's serum creatinine goes from .3 to, say, .7, that's a 4 milligram per deciliter increase but may also represent a 50 percent decrease in their kidney function. So that might be something to consider.

DR. MURATA: And, Dr. Estrella, you had a question to the sponsor about this --

DR. ESTRELLA: In terms of the equation for the cystatin C GFR.

DR. MURATA: Does the sponsor have that data available at the moment?

DR. SZWARCBERG: It is a eGFR by cystatin adjusted for age, sex and race. I'll be happy to read the equation to you.

DR. ESTRELLA: Is that by the Lesley Stevens' equation?

DR. SZWARCBERG: Unfortunately, I don't have the name of the group that validated the equation, but I can -- I'd be happy to spell it out for you or pass it on to you.

DR. ESTRELLA: Sure.

DR. SZWARCBERG: Mr. Chairman, should I do that?

DR. MURATA: Yes, if Dr. Estrella is willing to receive it.

DR. COX: And then maybe Dr. Estrella can describe it to us, so the rest of us know.

(Laughter.)

DR. ESTRELLA: So there are several equations for cystatin C GFR that have been evaluated in the non-HIV-infected population, and this one pertains to one that was validated against a, quote, "gold standard" of GFR measurement. And what I was interested in was looking to make sure that it was actually adjusted for age, gender and race, and it does.

DR. MURATA: So does this address your question?

DR. ESTRELLA: Yes. Thank you.

DR. MURATA: Any additional comments for Question 3?

Yes, Dr. Lewis -- Dr. Wood.

DR. WOOD: I actually have a question for the FDA. For the safety cohort, the median on study duration was 60 weeks. Does the FDA -- can the FDA say, okay, we'd like to look at data where the median on study duration is 72 weeks for that safety cohort to see whether there's any change in the signal and then maybe for the 118 study that involves renal impairment, we'd like to see the data when there's a median on study duration of 24 weeks, again to see if there -- I'm just trying to figure out when you might relook at the data for the trials that have already been presented to see whether or not there is potentially any early change or shift in the safety signal that makes it look more safe or maybe causes more concern.

DR. LEWIS: Yes, as the applicant said,

these pivotal studies are longer than a year. Gilead has been extremely diligent in providing us with data at least on an annual basis for their clinical trials. So we usually get at the end of 96 weeks and then at the end of the next year until the study is completed, and we have the opportunity at any point in that timeline to change labeling, strengthen or amend recommendations.

I feel certain that they will probably provide interim results of the renal safety study if there's anything untoward.

DR. MURATA: Any additional comments?

(No response.)

DR. MURATA: So really, this is an easier one to summarize on my part, really driven by the two renal colleagues for the most part. It looks like the answer to A would be urine dipstick --

Yes, Dr. Lewis? You had a question

DR. LEWIS: Yes. Just from our committee members who are practicing HIV clinicians, I'd like to know if any of these renal monitoring proposals would prove a burden on the clinic or the

clinician.

DR. DASKALAKIS: Demetre Daskalakis. I'm going to voice the nos that are in the room. So most of us are shaking our head no.

DR. MURATA: Actually, I have a relevant question for our renal colleagues here. So the flip side of Dr. Lewis' other question would be we all -- those of us who are practicing physicians know what we have in the clinic.

In terms of the cystatin or other more sophisticated renal specialty-based assays, how available are those in a routine practice?

DR. HUNSICKER: We've seen practices out in the sticks of Iowa, or it's at the University of Iowa, and the rules are different. You can get a cystatin mail-out anywhere in the country. I think it's not cheap, but it's not super pricy.

I don't think that we should require this as a baseline. I think that you trigger it based on something that's happened on the creatinine that you're worried about. And if you see nothing else going on at all, you say I think this is just COBI,

but I want to reassure myself. Then you can get this one in that subgroup of patients.

You can get isotopic GFRs. We call that referring patients to the unclear medicine. I'm not sure that I actually am going to recommend that. It's very expensive, and it's probably a waste of time most of the time.

The other things that I talked about, glycosuria, you get on your dipstick. If you get a PCR, which I think is available anywhere, you want to make sure if you're ordering this thing that you don't get an ACR, an albumin creatinine ratio, because that's not going to help you with what you're interested in. You want a protein creatinine ratio. But I think you can get a protein creatinine ratio at essentially any hospital. And I think that that is easily available.

All the other things I talked about are basically research tools at this time. If it turned out that the thing that you really need to do is test for beta 2 microglobulin, which you can

do if you want -- but if it turns out that really is very important for the HIV community, within a few years it'll be on your laboratory thing, but it's not there now.

DR. MURATA: Does that answer the agency's question?

DR. LEWIS: Yes. Thank you.

DR. MURATA: So essentially, point A, urine dipstick, protein quantification, as Dr. Hunsicker just mentioned to you, protein creatinine ratio.

B, for renal safety enhanced by monitoring renal function, an emphatic yes by Dr. Hunsicker and Dr. Estrella.

And then C, for cutoffs, the issue has been raised about what the test to use such as cystatin and its availability in terms of the -- in addition, one of the points that was raised by our renal colleagues is that in addition to the proposed .4 mLs per deciliter increase or change, percent increase is another potential parameter for such renal functions.

We will move on to Question 4 for

discussion. Please discuss any postmarketing studies needed to further define risks or optimal use of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

DR. HUNSICKER: You've had a lot of discussion on this, and so I don't know we need to repeat it. I guess females, longer-term follow-up, clarification if the enhancers really change the tenofovir safety ratio, those would be the big things that I can think of.

DR. CHEEVER: Bone, you had mentioned earlier. Bone, looking at bone mineral density.

DR. HUNSICKER: Well, long-term follow-up particularly renal and bone.

DR. DASKALAKIS: I think embedded in renal should be studies looking at various modalities of measuring renal function. So adding not just a standard but a couple of other options to see if we have to change our standard.

DR. HUNSICKER: Not so much measuring renal function but early detection of tubulopathy.

DR. DASKALAKIS: I stand corrected, early

detection of tubulopathy. So definitely have multiple modalities embedded in these studies, especially in a diverse population like women to make sure that we know the best way to do this testing to identify early damage.

DR. MURATA: Dr. Cheever.

DR. CHEEVER: And I would add to that to sort of get a better sense of the timeline in terms of ordering these tests every three months if we need to continue to do that or what the ratio of when to order the tests. To catch it early, as was pointed out by renal colleagues several times, that we want to catch this as early as we can.

DR. MURATA: Dr. Daskalakis.

DR. DASKALAKIS: I think the another thing that came up was the use of the QUAD with a PI. I guess the other question is the use of the QUAD with other salvage drugs like potentially your salvage NNRTI like etravirine; is there something in the pipeline for that? That's something that I think people will be interested in because it would be a convenient once-a-day addition to a salvage

regimen.

DR. MURATA: Dr. Strader

DR. STRADER: Dr. Doris Strader. I know the sponsors said that they did some studies looking at oral contraceptives, but I don't know how many patients were in that study. And they mentioned in the discussion that the data that they had there cannot be extrapolated to other forms other than Ortho Tri-Cyclen. So I think that it probably should be looked at with respect to other OCPs in women as well.

DR. MURATA: Dr. Cheever.

DR. CHEEVER: We also mentioned earlier just looking at potential development of resistance to protease inhibitors, just given that we have these secondary mutations popping up, and maybe it's random and maybe it's not, and to better understand that.

DR. DASKALAKIS: One more also. I think there is a lot of community concern about metabolics and morphology issues. We said there wasn't a lot -- it's been a very short follow-up,

but having a sub-study of one of these that includes a specific look at metabolic markers beyond lipids as well as any sort of anthropometric body morphology changes associated with this drug.

DR. MURATA: Dr. Giordano.

DR. GIORDANO: I think you need a study to figure out what you're going to call this thing. Do you have a name, and if you don't, I propose QUADzilla?

(Laughter.)

DR. GIORDANO: What do you think? No? Okay.

DR. LEWIS: The review of the name is still in progress.

DR. MURATA: Let me quickly summarize the points that have been raised. As Dr. Hunsicker had mentioned, there was an extensive discussion of these PMCs in Question 1. And so let me try to reiterate many of them.

Longer-term follow-up, renal bone parameters; studies involving additional females; the QUAD with other antiretroviral including PI for

salvage regimens; As Dr. Strader and others have mentioned, oral contraceptives for the drug interactions; Dr. Cheever's comments about PI resistance during the subsequent and ongoing clinical studies; Mr. Raymond's question about anti-HCV medications, directly acting antivirals; Dr. Daskalakis' comment about metabolic profile changes while on therapy.

The sponsor previously mentioned other drug interaction studies that were in progress, including methadone and other narcotics, carbamazepine, ribavirin.

The question of the name is well taken.

Any other comments on discussion point 4?

(No response.)

DR. MURATA: Would the agency have any additional comments?

DR. BIRNKRANT: We just wanted to thank our advisory committee members for today's discussion. We find your input and recommendations quite valuable, and we'll take them under consideration as we continue our review processes.

I also wanted to thank Gilead Sciences for their participation today, as well as the open public hearing speakers. We appreciate your thoughts.

I would like to commend our FDA E/C/F/T multidisciplinary review team. They've done an outstanding job as has our advisors and consultant staff. And I also would like to thank Dr. Murata for doing an outstanding job as acting chair today.

(Applause.)

Adjournment

DR. MURATA: Thank you very much to the agency for inviting us and giving me the chance to serve as acting chair today.

We will now adjourn the meeting. Please remember to drop off your name badge at the registration table on your way out so they may recycle. Thank you.

(Whereupon, at 3:01 p.m., the meeting was adjourned.)