DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Antiviral Drugs Advisory Committee

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8:00 a.m.

The Inn and Conference Center
University of Maryland, University College
3501 University Boulevard East
Adelphi, Maryland

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PARTICIPANTS

Craig W. Hendrix, M.D., Acting Chair
Paul T. Tran, RPh., Designated Federal Official

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Craig W. Hendrix, M.D.
Victoria A. Cargill, M.D., MSCE
Robert M. Grant, M.D., MPH
Peter L. Havens, M.D., M.S.
Tracy Swan (Consumer Representative)

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Enrico P. Veltri, M.D.

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBER (Voting)

James Neaton, Ph.D.

CDER TEMPORARY VOTING MEMBERS (Voting)

Curt H. Hagedorn, M.D.
Michael Marco, MPH (Patient Representative)
Barbara H. McGovern, M.D.
Michelle E. Roland, M.D.
Doris B. Strader, M.D.
Russell B. Van Dyke, M.D.

REGULAR GOVERNMENT EMPLOYEES (Voting)

Dennis O. Dixon, Ph.D.
Alice K. Pau, Pharm.D.

FDA PARTICIPANTS (Non-voting)

Debra B. Birnkrant, M.D.
John Farley, M.D., MPH
Poonam Mishra, M.D.
Scott Proestel, M.D.
Jeffrey S. Murray, M.D.

C O N T E N T S

P R O C E D I N G S

Call to Order

DR. HENDRIX: Good morning. I'm Craig Hendrix. I am the Acting Chair of the Antiviral Drugs Advisory Committee and I will now call the meeting of the Antiviral Drugs Advisory Committee to order.

Introduction of the Committee

First, we will go around the room and ask the folks at the panel here to introduce themselves. We will start with the FDA and Dr. Farley, to my left, and then we will move around the table.

DR. FARLEY: Good morning, everybody. John Farley, Deputy Director of the Office of Antimicrobial Products at CDER.

DR. BIRNKRANT: Debbie Birnkrant, Director, Division of Antiviral Products, CDER, FDA.

DR. MURRAY: Jeff Murray, Deputy Director, Division of Antiviral Products.

DR. PROESTEL: Scott Proestel, Medical Team Leader, Antiviral Products.

DR. MISHRA: Poonam Mishra, Medical Officer,

Division of Antiviral Products.

DR. NEATON: Jim Neaton, a biostatistician from the University of Minnesota.

MR. MARCO: Michael Marco, patient representative. I am from Columbia University and the International Center for AIDS Care and Treatment Programs.

DR. CARGILL: Victoria Cargill, Director of Minority Research and Clinical Studies, Office of AIDS Research, NIH.

DR. GRANT: Robert Grant, clinical neurologist, Gladstone, University of California, San Francisco.

DR. HENDRIX: Craig Hendrix, Clinical Pharmacology at Johns Hopkins.

DR. TRAN: Paul Tran, Designated Federal Official for the Antiviral Drug Advisory Committee.

DR. HAVENS: Peter Havens, Pediatric Infectious Diseases, Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee, Wisconsin.

MS. SWAN: Tracy Swan, consumer representative and Co-infection Project Director of Treatment Action Group in New York City.

DR. PAU: Alice Pau, clinical pharmacist, NIAID,

NIH.

DR. ROLAND: Michelle Roland. I am Chief of the Office of AIDS at the California Department of Public Health.

DR. McGOVERN: Barbara McGovern. I am a clinician who takes care of HIV/Hep C co-infected patients, and I am affiliated with Tufts University.

DR. VAN DYKE: Russ Van Dyke, Pediatric Infectious Diseases at Tulane University, in New Orleans.

DR. DIXON: Dennis Dixon, biostatistician, NIAID, NIH.

DR. STRADER: Doris Strader, gastroenterologist and hepatologist, Fletcher Allen, Burlington, Vermont.

DR. HAGEDORN: Curt Hagedorn, professor of medicine, hepatologist, gastroenterologist at University of Utah Medical Center.

DR. VELTRI: Rick Veltri, Schering-Plough Research Institute. I am the industry representative.

DR. HENDRIX: Thank you. Before we begin the meeting, I would like to ask Dr. Birnkrant to make a special presentation.

FDA Opening Remarks

DR. BIRNKRANT: Good morning. I would like to welcome everyone to today's advisory committee meeting where we will be discussing Pfizer's supplemental new drug application for maraviroc for use in combination with other antiretroviral agents in treatment-naive HIV-infected subjects.

During the review of this application we noted some issues that we thought would be important to bring to a public advisory committee so we could get input from our panel of experts, and we will be delving into those issues soon after my remarks.

But before we get to that, I would like to acknowledge the members of our advisory committee who are rotating off and our new members who are joining us. Our new members are Dr. Barbara McGovern, Dr. Curt Hagedorn, Dr. Michelle Roland, Dr. Russell Van Dyke, Dr. Doris Strader and Dr. Susan Ellenburg who couldn't join us for today's meeting.

Those advisory committee members rotating off the committee include Dr. Marshall Glesby, Dr. Gail Demmler, Dr. Janet Anderson, Dr. Robert Grant and Dr. Peter Havens. Those who are rotating off the committee will be receiving

an Advisory Committee Service Award. Those who are not here will have their awards sent to them but those who are here can come up and receive their awards today.

So, I would like to acknowledge Dr. Grant in recognition of distinguished service to the people of the United States of America. Thank you very much for serving on our committee.

DR. GRANT: Thank you.

DR. BIRNKRANT: I would like to acknowledge Dr. Havens. Thank you also for serving on our committee. We appreciate your help.

DR. HAVENS: Thank you.

DR. BIRNKRANT: With that, I will turn it over to Dr. Proestel, Medical Team Leader in the Division of Antiviral Products, to introduce today's topic.

DR. TRAN: We will do the chair statement first and the conflict of interest. Thank you.

DR. HENDRIX: For topics such as those discussed at today's meeting there is 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 FDA about these proceedings, however, FDA will refrain from discussing the details of the 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 very much.

Conflict of Interest Statement

DR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the antiviral Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees 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 the federal ethics and conflict of interest laws covered by, butt not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic 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 Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, the

members and temporary voting members of this committee have been screened for potential financial conflicts 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's agenda involves discussions of an efficacy supplement for the new drug application, 022-128, Selzentry (maraviroc) 300 milligram tablets. Pfizer, Inc. is proposing a new indication for the treatment of antiretroviral-naive patients with chemokine receptor 5 tropic human immunodeficiency virus.

This topic is a particular matter involving specific parties. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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 hand.

With respect to FDA's invited industry representative, we would like disclose that Dr. Enrico Veltri is serving as a non-voting industry representative, acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any one particular company. Dr. Veltri is currently an employee of Schering-Plough.

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

FDA encourages all other participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue including consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the

meeting. Thank you.

DR. HENDRIX: Now we will proceed with the FDA opening remarks from Dr. Scott Proestel.

FDA Opening Remarks

DR. PROESTEL: Good morning. I also wanted to welcome the committee here today, as well as the other attendees to this meeting. We look forward to a very good discussion.

As I suppose you are all aware, maraviroc received the treatment-experienced indication, the accelerated approval, in 2007 and received traditional approval in 2008, and we are here to discuss the results of study 1026 which provides data for the treatment-naive indication. We are very glad that the company is continuing to develop drugs for this important indication.

We do have some key questions that we would like to ask the committee. One, in particular, has to do with the results of the primary endpoint. We will be discussing this later but what we observed was a relative increase in failure for the virologic endpoint for maraviroc and a relative increase in adverse events for efavirenz which led to overall similar results for the primary endpoint, and we

felt this was a very challenging question that we would like the committee to address.

So, without further ado, I believe Pfizer's Dr. Howard Mayer has a presentation today.

DR. HENDRIX: Before we do that, let me just add here that this is a meeting for public observation. The attendees from the public may not participate, except at the specific request of the panel. With that, let me go ahead and proceed to the sponsor's presentation. We are ready. I am sorry, go ahead.

Sponsor Presentation

Introductions, Background and Overview of Maraviroc's Role in Treatment-Naive Patients

DR. MAYER: Good morning, everyone.

[Slide]

I am Howard Mayer, the disease area lead for antiviral drug development at Pfizer. On behalf of Pfizer and the maraviroc team, I would like to thank the Division of Antiviral Drug Products at FDA for giving us the opportunity today to review the maraviroc data in treatment-naive patients infected with CCR5 tropic HIV-1.

[Slide]

This is the agenda for the presentations from Pfizer. I will begin with introductions, background on maraviroc, and discuss the role of maraviroc in treatment-naive patients.

I will then hand it over to Jayvant Heera, the global clinical lead for maraviroc, who will review the clinical efficacy in treatment-naive patients, followed by presentations from Mike Westby on preclinical and clinical virology. Jim Goodrich, the development team leader, will review the safety and toleration of maraviroc. Then I will close the session.

[Slide]

Currently, maraviroc is indicated, in combination with other antiretroviral agents, for the treatment of adult patients who are infected with only CCR5 tropic HIV-1 and who have evidence of viral replication in HIV strains resistant to multiple agents.

[Slide]

Our proposal is that this indication should be extended to include all patients, including antiretroviral-naive patients infected with only CCR5 tropic HIV-1, based on the data being presented today.

[Slide]

This shows the cumulative survival curves for HIV-1 infected patients in the pre-HAART era, in yellow; in the early HAART era, in dark orange; and in the late HAART era, in the light orange compared with population controls. HIV-infected patients have only a ten-year shorter expected survival compared with uninfected matched controls as of the late HAART era. Therefore, there is a need for well-tolerated agents that patients can remain on for decades and that don't cause or exacerbate comorbid conditions in an aging population.

As will be shown in today's presentations, maraviroc is not associated with either frequent discontinuations due to adverse events or with long-term safety issues that are characteristic of some of the current antiretroviral drug classes.

[Slide]

This summarizes the current Department of Health and Human Services and International AIDS Society-USA antiretroviral treatment guidelines and recommendations on when to initiate HAART. The pendulum has clearly swung back to earlier treatment over the last several years, and now it

is recommended to initiate HAART in all patients with CD4 counts of 350 or lower.

In addition, the guidelines state that consideration should be given to initiating therapy with even higher CD4 counts, particularly when there are comorbid conditions or other factors which could affect HIV disease progression, as is shown on this slide.

So, it is critical that agents are available which make it easiest for patients to adhere to over the long term and that don't contribute to these comorbid illnesses. We believe maraviroc could be a potential option that fills this need for patients.

[Slide]

It is, in fact, these patient populations who are arguably not optimally served by current initial therapeutic options. This includes patients with comorbid conditions such as cardiovascular disease; liver disease, notably hepatitis co-infection; neuropsychiatric disease and substance abuse; metabolic diseases, including diabetes; and patients with concurrent tuberculosis infection.

Other populations where current initial therapeutic choices may be challenging include women who are

pregnant or who want to become pregnant and are, therefore, not candidates for efavirenz, given its potential for teratogenicity.

Contrary to the need for agents that can be started earlier in the course of disease, navaropine is limiting in women with CD4 counts of greater than 250 cells due to the risk of liver toxicity.

Lastly, in the United States transmitted NNRTI resistance occurs in approximately 7 percent of patients and primary HIV resistance overall can be as high as 15 percent in certain locations. These patients have a greater likelihood of failing currently preferred first-line therapy.

[Slide]

To determine the prevalence of baseline minority variants that are not detected by standard resistance testing 205 patients who were antiretroviral naive and who had no detectable resistance mutations by routine testing were assayed by sensitive real-time PCR. At least one minority drug resistance mutation was identified in 17 percent of the patients. Multi-drug resistance mutations were uncovered in 2 percent.

To assess the clinical impact of these minority resistant variants, in a separate group of 316 patients who participated in two studies which evaluated efavirenz, lamivudine plus either abacavir or zidovudine, 9 patients overall had baseline minority variants and 7 of 9 of those patients with detected baseline minority variants experienced virologic failure. This indicates that transmitted drug resistant virus to existing classes is frequent, underestimated by standard genotype, and is associated with an increased risk of virologic failure.

[Slide]

While virus tropism phenotype is a newer concept than resistance to existing antiviral drug classes which I just presented the principles are similar. Maraviroc is active against R5 virus, that is, virus that enters the cells through the CCR5 receptor, as shown in the upper right in red.

R5 virus only is found in the majority of treatment-naive patients approximately 75-80 percent of the time. However, preexisting and currently maraviroc insensitive virus populations, that is, virus capable of using the CXCR4 receptor for entry, can exist in several

different forms.

[Slide]

First, as pure X4 virus, as shown in green on the upper left or, second, as dual tropic virus, that is, virus capable of utilizing either receptor for entry, as shown in the upper middle portion of the slide in blue, and which generally exists as a mixed tropic population of purely CCR5- or CXCR4-using virus mixed with dual tropic variants, as shown on the lower half of the slide, collectively confer an increased risk of virologic failure on maraviroc compared with those patients who have purely R5 virus and who, therefore, are most likely to respond to a maraviroc-based regimen.

[Slide]

This is what was observed in the maraviroc treatment-naive study utilizing the original Trofile phenotypic assay set at a certain threshold to detect and exclude patients with minority X4 variants that was not yet informed by long-term clinical trial data with maraviroc.

[Slide]

The original phenotypic assay used in the treatment-naive study to exclude patients with CXCR4-using

virus detected X4 clones down to 5-10 percent of the total viral population with 100 percent sensitivity.

[Slide]

However, that original assay is no longer available and has been replaced by an improved assay capable of detecting minority X4 variants with 30-fold greater sensitivity, down to 0.3 percent of the total virus population.

And, as one would predict based on the data I presented earlier regarding the impact of minority resistant variants on clinical outcome with an efavirenz-based regimen, the detection of low-level X4 variants by an improved diagnostic test identified patients who were at greater risk of virologic failure on maraviroc, and excluding them from the analysis had a significant impact on response rates to a maraviroc-based regimen. Later this morning Dr. Jayvant Heera will present these results in detail.

[Slide]

A phase 3 development program with maraviroc was conducted in both treatment-naive and treatment-experienced patients. As you have heard today, we are here to review

the treatment-naive study which compared maraviroc with efavirenz, both in combination with fixed dose zidovudine/lamivudine in patients with R5 virus.

The co-primary endpoint was the percent of patients who achieved an HIV RNA less than 400 and less than 50 copies/ml at week 48, and 721 patients were enrolled into the maraviroc twice daily and efavirenz treatment groups, and 360 patients received maraviroc 300 mg twice daily.

[Slide]

However, I would first like to briefly review the data in treatment-experienced patients. We conducted two identical trials in treatment-experienced patients with R5 virus in different geographic locations. These were superiority studies comparing maraviroc to placebo, combined with an optimalized background regimen. Nearly 1,100 patients were enrolled, with 840 receiving maraviroc.

[Slide]

The efficacy data from the maraviroc treatment-experienced studies need to be seen in the context of the time when they were conducted. The recently approved drugs which provide significant efficacy in treatment-experienced patients with multi-drug resistant virus, darunavir,

raltegravir and etravirine, were not available to patients in this study.

Yet, despite that, nearly 50 percent of patients achieved an HIV RNA less than 50 copies/ml at week 48, almost 3 times that in the placebo group. This significantly greater response rate on maraviroc was maintained regardless of high or low CD4 count, high or low screening viral load, and this effect was maintained through two years of therapy.

[Slide]

In the maraviroc studies CD4 cell count increases have been observed where they were not necessarily expected. As shown in the graph on the left, in a phase 2b study conducted in patients known to have dual/mixed tropic virus who, as expected, did not benefit virologically the median CD4 count increases were greater in patients receiving maraviroc compared with placebo.

In the pivotal treatment-experienced studies conducted in patients with R5 virus, as shown in the graph on the right, a significantly greater median increase in CD4 cell count was observed in patients who received maraviroc compared with patients who received placebo. This greater

rise in CD4 cell count on maraviroc was also seen in the treatment-naive study and will be discussed by Dr. Heera in his presentation.

[Slide]

The clinical relevance of these CD4 count findings is unclear at this time. However, while there was concern at the time of maraviroc's initial approval regarding the potential negative effects on immune surveillance, in the treatment-experienced registrational studies, there was a significantly lower incidence of malignancies overall, AIDS-defining and non-AIDS-defining malignancies, as well as potentially infection-related and non-infection related malignancies. The lower incidence of malignancies on maraviroc was also observed in the treatment-naive study, as will be described by Dr. Goodrich later this morning.

[Slide]

In addition, there was concern at the time of maraviroc's initial approval regarding hepatotoxicity as a potential class effect, given cases of Hy's law observed with aplaviroc, a CCR5 antagonist being developed by GlaxoSmithKline that was ultimately terminated from development.

As shown here, exposure-adjusted incidence of grade 3 and 4 liver enzyme abnormalities, at week 96 in the maraviroc treatment-experienced studies demonstrates no evidence of an excess in transaminase abnormalities or in bilirubin on maraviroc compared to placebo. These findings are consistent with those in the treatment-naive study and in other maraviroc trials, as will be discussed by Dr. Goodrich later this morning.

[Slide]

In summary, the presentations that follow will show that the maraviroc data in treatment-naive patients confirm the safety and efficacy data which was observed in treatment-experienced patients. As in the treatment-experienced studies, maraviroc demonstrated durable antiviral activity, in this case when compared with standard of care in treatment-naive patients; is safe and well tolerated, with no safety issues consistently associated with the drug; offers a potential treatment option suited to a changing HIV treatment paradigm with earlier treatment and an aging HIV population; and expands patient treatment options based on its unique mechanism of action.

With that, I will turn this over to Dr. Heera who

will present the clinical efficacy data.

Study A4001026 Efficacy

DR. HEERA: Thank you, Dr. Mayer. Good morning, ladies and gentlemen.

[Slide]

I will be presenting the clinical efficacy data of study 1026. This is a schematic representation of study 1026 trial design which was a randomized, double-blind, controlled study of maraviroc in treatment-naive patients. Study eligibility criteria included an R5 tropism determined using the original Trofile assay, as well as the absence of resistance to efavirenz, zidovudine or lamivudine.

There were 721 patients who were randomized in a 1:1:1 ratio to receive either maraviroc 300 mg twice daily or efavirenz 600 mg once daily in combination with zidovudine and lamivudine, which was the standard of care at the time of initiating the study in November of 2004. The primary analysis time point was at week 48 and patients were stratified at the time of randomization by screening viral loads less than and greater than 100,000 copies/ml and by geographic region.

The maraviroc 300 mg QD arm was discontinued at

the end of phase 2b for failure to meet prespecified non-inferiority criteria. This is an ongoing study and secondary analyses demonstrating durability of response will be presented on blinded data through 96 weeks.

[Slide]

In the treatment-experience clinical trials the most commonly observed virologic correlative failure was the unmasking of a preexisting CXCR4-using virus. The hypothesis that led to a blinded analysis with the more sensitive assay was that better detection of CXCR4-using virus would decrease failures that are associated with emergence of CXCR4-using virus.

Following the original primary analysis a critical development occurred in the field of tropism diagnostics in June of 2008 when Monogram Biosciences replaced the original Trofile assay which was used to screen patients into the study with an enhanced version for clinical use. As described by Dr. Mayer, the enhanced assay has greater sensitivity to detect CXCR4-using virus compared to the original Trofile assay. Throughout this presentation the enhanced sensitivity Trofile assay will be referred to as ESTA.

In order to ensure that this process remained objective Monogram bioscientists were blinded to treatment outcomes and to treatment assignments. Screening samples were tested in all 621 patients who received at least one dose of study medication, and key analyses were prespecified by Pfizer in a statistical analysis plan.

[Slide]

This slide provides a breakdown of patients who were reclassified with CXCR4-using virus by ESTA, shown in the second row, and patients with CCR5 tropic virus, shown in the last row. Of the 721 patients who received at least one dose of study medication, there were 107 patients who were reclassified with CXCR4-using virus that made up approximately 15 percent of the population. Forty-nine of these patients were in maraviroc arm and 58 in the efavirenz arm. The remaining 614 patients were confirmed to have CCR5 tropic virus by ESTA and 311 patients were in the maraviroc arm and 303 were in the efavirenz arm.

[Slide]

This slide compares baseline and demographic characteristics for the original Trofile and ESTA population, and shows that overall these characteristics

were balanced between the treatment groups and between the populations. Baseline prognostic characteristics were also looked at in patients excluded by ESTA with CXCR4-using virus and these were also comparable between treatment groups and between populations. Across the populations we analyzed the mean age was approximately 37 years, with 29 percent of participants being female and 45 percent non-white. The median CD4 cell count was 250 cells and the mean HIV-1 RNA was 4.9 logs.

For the primary analysis I will present outcomes in both the prespecified original Trofile population and the ESTA population. I will focus on the ESTA analysis population for all efficacy data subsequent to the original primary endpoint.

[Slide]

Now, the primary endpoint of this study was the difference between maraviroc and efavirenz in the percentage of patients with viral loads less than 400 and less than 50 copies/ml at week 48.

This study was a non-inferiority study that was designed to show that the antiviral activity of a maraviroc-containing regimen was similar or comparable to that of an

efavirenz-containing regimen. This means that in order to conclude non-inferiority the lower bound of the 97.5 percent confidence interval for the difference between maraviroc and efavirenz in the proportion of patients achieving a week 48 viral load less than 400 and less than 50 copies/ml should be above -10 percent.

Firstly, this slide is a graphical representation of the more stringent co-primary endpoint of less than 50 copies/ml, which is the more commonly used efficacy measure. In the original Trofile population you will note that there was a small stratification-adjusted treatment difference of -4.2 percent with the lower confidence bound falling just outside of the -10 percent non-inferiority margin.

However, in the ESTA population treatment differences were narrowed, with approximately 68 percent of patients achieving undetectable viral loads in both treatment groups. The stratification-adjusted treatment difference was -0.2 percent, with the lower confidence bound now falling within that -10 percent margin at -7.4 percent.

[Slide]

For the less than 400 copies for the co-primary endpoint, shown on the right-hand side of this slide, non-

inferiority was demonstrated in the original Trofile population and, as would be expected, in the ESTA population treatment differences were narrowed, with 73.3 percent of patients achieving viral loads less than 400 copies on the maraviroc arm, and the lower confidence bound remained within the -10 percent margin.

In summary, for the primary endpoint in the ESTA population the lower confidence bound for the treatment differences fell within the non-inferiority margin for both the less than 400 and the less than 50 copies/ml endpoints.

[Slide]

We also explored outcomes in patients who were excluded from the ESTA population to ascertain that based on our hypothesis these patients were at a higher risk of virologic failure on maraviroc but not on efavirenz.

Shown on the left-hand side of this slide are treatment responses in maraviroc recipients and the response in maraviroc patients who had CXCR4-using virus was 45 percent compared to 69 percent in those maraviroc patients with CCR5 tropic virus.

Of note here is the fact that patients on efavirenz, shown on the right-hand side, had similar

responses regardless of whether or not they were reclassified with the ESTA assay. Also to note is that efficacy on maraviroc was the only outcome that was shown to improve. Overall, no other outcomes were shown to have significantly changed in the ESTA analysis. Taken together, these data serve as compelling validation that the ESTA appropriately excluded patients who were less likely to respond to maraviroc.

[Slide]

Now, to ascertain whether the potency of maraviroc is comparable to efavirenz patients who started the trial with high viral loads we compared treatment responses in the two treatment groups at week 48. Overall, for patients with screening viral loads greater than or less than 100,000 copies/ml a similar percentage of patients in each treatment group achieved undetectable viral loads at week 48.

[Slide]

And in order to demonstrate the durability of response on maraviroc, secondary analyses were performed to compare responses in each treatment group at week 96. The analysis shown on this slide is a pre-planned secondary analysis at 96 weeks, and confidence intervals are shown for

descriptive purposes.

It shows that similar virologic responses were maintained at 96 weeks, with 59 percent of patients on maraviroc and 63 percent of patients on efavirenz achieving undetectable viral loads at week 96.

[Slide]

We also then performed an analysis using the FDA-defined time to loss of virologic response algorithm, also known as TLOVR, which requires patients to have two consecutive viral loads greater than 50 copies/ml.

This is shown on the right-hand side and confirms that a similar percentage of patients or 61 percent in both treatment groups achieved viral suppression at week 96. Among those patients who had one detectable viral load greater than 50 copies/ml at 96 weeks, there were 9 of 11 maraviroc patients and only 1 of 3 efavirenz patients who maintained viral suppression below 50 copies/ml following week 96.

Taken together, these analyses confirmed that the durability of virologic response was similar in patients who received efavirenz and maraviroc.

[Slide]

We looked at outcomes in patients who were followed in the study after discontinuing to determine whether patients were able to achieve viral suppression on their subsequent regimens. This slide summarizes the percentage of patients who achieved undetectable viral loads following discontinuation, and shows that approximately 60 percent of patients who discontinued in each arm achieved confirmed viral load suppression at or beyond 16 weeks after study drug discontinuation.

These data suggest that patients who discontinued maraviroc were able to achieve viral suppression on a subsequent regimen, similar to what is observed in patients who discontinued an efavirenz-containing regimen.

[Slide]

This slide is a graphical representation of the median increases in CD4 cell counts from baseline through the first 48 weeks of the study. There were faster and larger median increases in CD4 cell counts on maraviroc compared to efavirenz through 48 weeks, with a treatment difference of 27 CD4 cells in favor of maraviroc at week 48.

[Slide]

The greater median increases in CD4 cell counts on

maraviroc were maintained through 96 weeks, with a treatment difference of 29 CD4 cells in favor of maraviroc at week 96. As described by Dr. Mayer, these findings have also been consistently demonstrated through previous studies across the maraviroc development program.

[Slide]

Shown on this slide is an analysis of patients who started the trial with CD4 counts below 200 cells whose CD4 cell rises on the study exceeded clinically relevant CD4 cell thresholds through week 96. The percentage of patients with CD4 cell rises that exceeded 200 cells, 350 cells and 500 cells are shown in the left, middle and right-hand bars respectively.

Now, these patients had all started the trial with a risk of developing AIDS-defining illnesses due to severe immunosuppression, with CD4 counts below 200 cells. The data on the left-hand side demonstrates that 80 percent of maraviroc patients who started with CD4 cell counts below 200 cells achieved and exceeded a CD4 cell count greater than 200 cells, thus, removing them from that risk group of developing AIDS-defining illnesses, compared to 64 percent of patients in the efavirenz treatment group.

This difference was shown to be statistically significant. Similarly, more patients on maraviroc achieved and exceeded CD4 thresholds greater than 350 and greater than 500 cells.

[Slide]

In summary of the efficacy data I have presented in study 1026 with regards to the primary endpoint of the study in the ESTA analysis population, the lower bound of the confidence interval for the 48-week treatment differences for both the less than 400 and less than 50 copies/ml endpoints were above the -10 percent non-inferiority margin.

Secondary analyses confirmed the durability of maraviroc's virologic response through week 96. Faster and larger increases in CD4 cell counts on maraviroc were shown to be maintained through week 96, with more maraviroc patients exceeding clinically relevant CD4 cell count thresholds through week 96. Also, patients who discontinued maraviroc were able to achieve viral suppression similar to patients who discontinued an efavirenz-containing regimen.

I will now hand over to Dr. Mike Westby to discuss the virology data.

Study A4001026 Microbiology

DR. WESTBY: Thank you, Dr. Heera. Good morning, ladies and gentlemen.

[Slide]

I will begin my presentation this morning with a brief introduction to outline what we mean by mechanisms of virologic failure, and briefly summarize the current knowledge about these mechanisms with regard to maraviroc-containing antiretroviral regimens in treatment-experienced patients. I will then present the findings of our analyses in treatment-naive patients, specifically study 1026.

[Slide]

Virologic failure to any antiretroviral drug regimen, that is, an inability of the regimen to fully suppress viral replication in the plasma, often correlates with selection of viruses with resistance to one or more components of that regimen. This is typically detected by performing resistance tests on virus obtain from the patient at the time of virologic failure. These tests are either genotypic, that is, based on analysis of viral sequence, or phenotypic, that is, based on the amount of drug required to inhibit virus growth in tissue culture.

Another correlate of virologic failure that has been well described is the patient's failure to adhere to the prescribed antiretroviral medication. In large outpatient studies, such as 1026, observed dosing is not performed and so poor adherence has to be inferred.

[Slide]

Three mechanisms associated with virologic failure to maraviroc have been described in treatment-experienced patients enrolled in studies 1027 and 1028. Firstly, the detection of CXCR4-using virus. As described by Dr. Mayer, virus that can use CXCR4 as its entry co-receptor cannot be inhibited by maraviroc and so is not truly insensitive. Clonal analyses of viruses in patients failing maraviroc with CSCR4-using virus indicated that this virus preexisted maraviroc treatment and only became the dominant species when maraviroc inhibited the CCR5 tropic variants.

Secondly, CCR5 tropic virus that is resistant to maraviroc. Maraviroc resistant virus can use CCR5 as its entry co-receptor even when maraviroc is bound to that receptor. This is characterized in phenotypic drug susceptibility assays by viruses that cannot be fully inhibited by maraviroc.

Thirdly, poor adherence to the antiretroviral drug regimen. This is characterized by patients who had no evidence of maraviroc in their plasma during PK analysis and also likely failed with drug-sensitive CCR5 tropic virus.

[Slide]

I will now move on to describe the analyses we performed to characterize virologic failure in 1026.

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Resistance testing is reported for all drugs in the regimen at the time of virologic failure for patients whose viral load was sufficiently high to perform a valid test. CXCR4-using virus was identified using the Trofile assay, and maraviroc resistance virus for CCR5 tropic viruses was determined using the PhenoSense entry assay. Resistance to efavirenz, lamivudine and zidovudine was assessed genotypically using IAS USA resistance tables.

[Slide]

In order to understand the mechanisms of resistance we censored non-virologic failures and focused our analyses on 29 patients on maraviroc and 13 patients on efavirenz where full data sets were available.

[Slide]

These graphs show the percentage of patients failing maraviroc on the left and efavirenz on the right who had resistance to any drug in the regimen. As shown by the pink bars, 18 of 29, or 62 percent, of patients failing the maraviroc arm by week 48 had virus that was resistant to at least one component of their regimen compared to 10 of 13, or 77 percent, of patients failing the efavirenz arm.

As shown here in yellow, there were 9 failures in the maraviroc arm with CXCR4-using virus and 4 patients failing with CCR5 virus that was resistant to maraviroc. Collectively this accounts for 45 percent of the patients failing therapy on the maraviroc treatment arm and, thus, approximately half of the maraviroc patients failed with virus that was sensitive to maraviroc.

The majority of patients failing efavirenz did so with efavirenz resistance, as is shown by the gray bar, and 9 of the 10 patients with virus resistant to at least one drug had efavirenz resistant virus.

Lamivudine resistance, shown here in green, was detected in approximately two-thirds of the patients failing in the maraviroc treatment arm compared to approximately one-third of the patients in the efavirenz arm. Viruses

with either type of maraviroc resistance were also resistant to lamivudine, and all but one efavirenz-treated patient with virus resistant to lamivudine showed resistance to efavirenz. Finally, as shown in blue, few patients failed either arm with zidovudine resistant virus.

In summary, resistance to lamivudine was the correlate most commonly detected in the maraviroc arm, whilst efavirenz resistance was the resistance correlate most commonly detected in the efavirenz arm.

[Slide]

In order to understand why few patients on efavirenz failed with RT resistance we looked at resistance data and time to discontinuation for all patients whose virus was never suppressed.

This graph shows the cumulative percent of patients on the Y axis by time to last on-study treatment dose on the X axis for all patients who discontinued maraviroc in yellow, or efavirenz in grey, never having a confirmed viral load suppression below 50 copies/ml.

Closed symbols are patients in whom RT resistance was detected before discontinuation for any reason. The dotted vertical line is the week 8 time point. In either

group resistance virus was not detected in patients discontinuing prior to week 8. However, by this time point 80 percent of the efavirenz-treated patients had discontinued mainly for adverse events.

After week 8 a similar proportion of patients failing in each arm did so with resistant virus, but more patients were on treatment for longer in the maraviroc arm so the total patients with RT resistance was greater in that arm than in the efavirenz group, 17 versus 6 respectively. Therefore, the majority of patients who failed efavirenz never having suppressed their virus discontinued before resistance could be detected.

In order to understand the potential consequence of RT resistance of failure in the maraviroc arm we looked at data for all patients discontinuing with RT resistant virus for whom we had sufficient follow-up data and a documented next treatment regimen.

[Slide]

Shown on this graph is the percent of patients with RT resistant virus who achieved less than 50 copies on a subsequent therapy. Eight of the 11 patients, or 73 percent, who failed the maraviroc regimen with lamivudine

resistance achieved virus less than 50 copies on their subsequent regimen, indicating that despite failing their first regimen most were able to build an effective second regimen.

[Slide]

Focusing solely now on patients failing maraviroc with CCR5 tropic virus, approximately half of the patients, 11 of 20, had no resistance markers to any component of the regimen at failure. We believe that this is a consequence of poor adherence to therapy as we will now illustrate using PK data obtained during the first 48 weeks of study.

[Slide]

Shown on this slide is the cumulative predicted average plasma concentrations or C-average for maraviroc 300 mcg BID doses for the patients in the phase 1 and 2a studies where dosing was carefully monitored. These curves serve as a useful benchmark for where we would predict the cumulative C-average curve should appear in study 1026 where dosing was not observed and maraviroc was given without regard to food intake.

[Slide]

As expected, the cumulative C-average curve for

the maraviroc ESTA population, shown here in yellow, falls for the most part in between the fed and fasting curves. However, there is a tail where a number of patients had lower than expected C-average.

[Slide]

Looking at these patients in more detail we noted that many had PK visits where the amount of maraviroc in the plasma was below the limit of detection, or BLQ, which means it was less than 0.5 ng/ml. Patients in whom at least one BLQ measurement was recorded were then plotted as shown.

[Slide]

You can see that they fall to the lower end of the concentration distribution. From our phase 1 and 2a data we estimate that for this to happen a patient would have to miss at least 3 consecutive doses of maraviroc immediately prior to a study visit. We, therefore, used this as a conservative and objective marker for poor adherence to medication.

[Slide]

When we identify on the plot those patients who failed with lamivudine resistance, shown here as M184V, you can see that they fall on the curve with the majority of

patients. However, we see a very different pattern when we look at the patients who failed with virus that has no resistance either to maraviroc or the reverse transcriptase inhibitors. As you can see, half have drug levels BLQs suggesting that they are non-adherent. A third of 3 patients with low C-average, shown here, had spiky plasma load profiles, suggesting they too were poorly adherent. Thus, a reason for failure on maraviroc without resistant virus appears to be poor adherence.

[Slide]

Finally, we have looked to see if there is an increased burden of resistance through 96 weeks. As shown here, only small numbers of additional patients failed each arm with resistance at the time of failure. Two patients failed maraviroc with RT resistance and 5 patients failed efavirenz with RT resistance.

[Slide]

So, in summary, lamivudine resistance was the most common virologic observation at failure in the maraviroc treatment group. We have shown that most patients with lamivudine resistance on follow-up are able to re-suppress on their subsequent regimen. Poor adherence to the regimen

accounted for approximately half of all patients who failed with R5 virus in the maraviroc group.

[Slide]

Maraviroc resistance virus was uncommon at failure, and since this is the first in-class agent it does not lead to cross resistance to any other approved antiretroviral drug.

[Slide]

Finally, efavirenz resistance was the most common virologic observation at failure, as has been described in other similar studies.

I will now hand you over to Dr. Goodrich who will take you through the safety and toleration data.

DR. TRAN: I just want to make a quick announcement for our presenters. If you would refrain from bringing your blackberries or cell phone to the podium to not interfere with the microphone system.

Study A4001026 Safety

DR. GOODRICH: Good morning, ladies and gentlemen.

[Slide]

It is my privilege to present to you study A4001026 96-week safety data. These data include all

patients randomized and receiving at least one dose of study drug, followed through week 96.

The design of the 1026 study, having an active comparator with fixed background therapy in patients with less advanced HIV disease, provides valuable information on the safety and toleration profile of maraviroc in a population with fewer confounding factors when compared with the treatment-experienced studies A4001027 and A4001028.

Today I want to discuss briefly the overall safety and toleration of maraviroc, hepatic safety, category C events, malignancies, cardiac safety and lipid profile.

[Slide]

There are now 9,707 patient-years of exposure to maraviroc versus 526 patient-years of exposure available at the time of the accelerated approval for treatment-experienced patients. This allows greater overall confidence in the safety profile of maraviroc in comparison to the initial filing.

The maraviroc exposure data is based on the current study, A4001026, under review today, the treatment-experience program which consisted of studies 1027 and 1028, the expanded access program, postmarketing surveillance and

additional maraviroc studies.

[Slide]

Let's move on to the safety and toleration of maraviroc in comparison to efavirenz. Approximately 94 percent of patients in each treatment arm experienced some adverse event. The most frequently reported adverse events seen in maraviroc patients were nausea, headache, dizziness, diarrhea, fatigue and upper respiratory tract infection. The frequently reported adverse events in patients in the efavirenz arm were nausea, headache, diarrhea, fatigue, dizziness, upper respiratory tract infection and vomiting.

When we turn our attention to discontinuations due to adverse events, both all causality and treatment related, there is a marked difference between the maraviroc and the efavirenz arms. There were 27 patients in the maraviroc arm versus 67 patients in the efavirenz arm that discontinued due to all causality adverse events. This proportion of discontinuations in treatment arms was maintained for patients discontinuing due to treatment-related adverse events.

The discontinuations in the efavirenz arm occurred earlier over the course of treatment, as shown by Dr.

Westby. There were also less patients with grade 3 and 4 serious adverse events in the maraviroc arm versus the efavirenz arm.

Category C events were similar between both arms while there were less malignancies in the maraviroc versus efavirenz arm. There were few deaths in the study and no imbalance between the treatment arms.

[Slide]

When we look at key adverse events leading to discontinuation there were 27 patients in the maraviroc arm and 67 patients in the efavirenz arm permanently discontinued from the study due to all causality treatment-emergent adverse events. There was an increase in nervous system, psychiatric, skin and subcutaneous and gastrointestinal disorders leading to discontinuation, as reflected in the efavirenz arm.

The nervous system category contains the terms for dizziness and includes 8 patients. There were multiple CNS adverse events within the psychiatric category, and 10 patients discontinued from the efavirenz arm due to rash.

[Slide]

The summary of safety and toleration of maraviroc

and efavirenz: Fewer patients in the maraviroc arm were discontinued due to adverse events, treatment-related adverse events. There were a greater number of efavirenz patients with grade 3 and 4 adverse events. And, maraviroc safety and toleration profile remains clinically distinct.

[Slide]

As mentioned previously by Dr. Mayer, there were questions about hepatotoxicity as a class effect of CCR5 antagonist. This slide looks at the proportion of patients with grade 3 or 4 liver test without regard to baseline at 96 weeks in study 1026.

Overall, there were fewer patients with elevations in liver test in both arms. There was no difference between the two arms for both AST and ALT test. Three patients on the maraviroc treatment arm had grade 3 bilirubin values, and no patient had a grade 4 bilirubin value. The grade 3 elevations were all due to elevations in indirect bilirubin and were not accompanied by rises in transaminases.

[Slide]

Now looking at the incidence of hepatic adverse events, there were more than twice the number of hepatic adverse events on efavirenz in this study as compared with

maraviroc. There were 15 events on efavirenz reported in 13 subjects and 6 events on maraviroc reported by 5 subjects.

[Slide]

In summary of hepatic safety, grade 3 and 4 ALT abnormalities have been consistently low across studies 1026, 1027 and 1028, as shown by Dr. Mayer in his introduction. There have been no hepatic events characterized by systemic allergic response, eosinophilia, increased IgE and hepatitis in HIV-positive subjects across the maraviroc program. Long-term follow-up suggests no increased risk of hepatic events in patients receiving maraviroc.

[Slide]

As mentioned in the introduction, there were questions with CCR5 inhibitors and the risk of infections and malignancies. When we look at infections that are characterized by deficiencies in cell-mediated immunity there are similar number of patients in the maraviroc arm versus the efavirenz arm with category C AIDS-defining illnesses during this study.

Tuberculosis accounted for 9 of all category C events in both arms. Eight were in the efavirenz arm versus

one in the maraviroc arm. None of the patients in the efavirenz arm who had an adverse event of tuberculosis had a previous history of TB. There were 5 cases of lymphoma, 2 in the maraviroc arm and 3 in the efavirenz arm, and 1 case of Kaposi's sarcoma in the efavirenz arm.

[Slide]

A second question about CCR5 antagonist was the question about an increased risk of malignancy. As can be seen from this slide, fewer patients receiving maraviroc reported malignancy-related adverse events when compared with the efavirenz arm.

[Slide]

An additional question at the time of the first filing was about cardiac safety, in which there was an imbalance between the maraviroc versus placebo arms for ischemic heart disease although the majority of the events were angina. These observations were complicated by the overall increased duration and exposure to drug in the maraviroc arms, and the 2:1 randomization of the maraviroc arm versus placebo.

The overall incidence of cardiac ischemic events was low in both treatment arms. Two patients in each

treatment arm had adverse events of myocardial infarction during the study. Other cardiac events were balanced between the two arms. Therefore, in this study maraviroc does not appear to be associated with any greater risk for cardiac ischemic events when compared with efavirenz.

[Slide]

In addition, when we look at changes from baseline in lipid parameters at week 96 the median changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels were greater in the efavirenz treatment group than in the maraviroc treatment group. The median decrease in the total cholesterol to HDL ratio was greater in the maraviroc group than in the efavirenz group.

[Slide]

In summary, fewer patients experienced discontinuations due to grade 3 and 4 adverse events in the maraviroc than in the efavirenz arm. Grade 3 and 4 transaminase elevations were infrequent and occurred at a similar rate in the two treatment arms. Hepatic adverse events were more common on efavirenz.

Category C events and malignancies in the

maraviroc arm were comparable with efavirenz and in the case of malignancies slightly less. Cardiovascular ischemic events were balanced between treatment arms, and maraviroc has a neutral effect on lipids when compare with efavirenz.

Thank you. Dr. Mayer will conclude our remarks.

Conclusions

DR. MAYER: Before summarizing I would like to update the committee on additional ongoing studies with maraviroc.

[Slide]

Pfizer-sponsored studies include long-term follow-up of the registrational studies in treatment-naive and treatment-experienced patients; an expanded access program; a 3,000 patient safety registry study in treatment-experienced patients; a study in hepatitis co-infected patients; a study in pediatric patients; and an NNRTI-sparing study in treatment-naive patients.

Investigator-initiated studies include the ACTG 5241 which is evaluating the use of maraviroc and other recently approved drugs for patients with multi-drug resistant HIV and whether the addition of NRTIs is required in this population.

The TERCET study is also studying the use of maraviroc as part of a novel regimen in treatment-experienced patients. Finally, two studies are evaluating the addition of maraviroc to a HAART regimen in advanced treatment-naive patients to determine whether the drug reduces the incidence of IRIS, or immune reconstitution inflammatory syndrome, compared with HAART alone, and to determine whether the addition of maraviroc reduces the incidence of AIDS, non-AIDS defining illnesses and death in this patient population.

[Slide]

In support of maraviroc's approval for treatment-naive patients maraviroc demonstrated durable antiviral activity, comparable to standard of care, at two years of follow-up. Increases in CD4 count over and above that seen with standard of care is consistent with the paradigm shifting towards earlier treatment given the greater likelihood of detecting R5 virus only.

It can effectively treat patients with primary drug resistance due to its novel mechanism of action, and expands patients' treatment options with a novel class which does not compromise future treatment options. Patients who

discontinued on maraviroc in study 1026 were as likely to suppress on their next treatment regimen as compared with efavirenz.

[Slide]

Maraviroc provides an important additional option, particularly for those patient populations who are not well served by currently approved first-line agents. Maraviroc can be used in patients with cardiovascular disease. There appears to be no increased risk of ischemic heart disease on maraviroc, and no safety signal was detected by FDA based on AERS data and data-mining of postmarketing reports.

[Slide]

Maraviroc is also a potential option for patients with coexisting liver disease. There has been no consistent evidence of hepatotoxicity with maraviroc and no safety signal was detected in postmarketing surveillance.

[Slide]

There has also been no evidence of negative effects on immune surveillance associated with an increase in either infections or malignancies, a concern in the aging HIV population. Again, this was not observed by FDA in postmarketing surveillance.

[Slide]

Patients with underlying psychiatric illness who may not be candidates for efavirenz could also use maraviroc.

[Slide]

In addition, maraviroc does not appear to cause or exacerbate hyperlipidemia or other metabolic diseases.

[Slide]

Expanding treatment options for women has been a challenge. Maraviroc has been shown to be efficacious, safe and well tolerated in women, and has a pregnancy category B classification.

[Slide]

Lastly, maraviroc can be used in patients who are co-infected with tuberculosis and require concomitant treatment.

[Slide]

In summary, based on data from study 1026, including an analysis of exposure response and supported by other clinical trial data and the postmarketing experience, a 300 mg twice daily dose of maraviroc is recommended to be used in combination with two NRTIs in treatment-naive

patients. The sponsor, therefore, proposes that the indication for maraviroc, in combination with other antiretroviral agents, should be expanded to include all adult patients infected with CCR5 tropic HIV-1. Thank you.

Questions of Clarification to Sponsor

DR. HENDRIX: Thank you very much. At this time we are going to take clarifying questions from the committee for the sponsor so these questions are limited to clarifying questions. We will have our discussion later this afternoon. Dr. Pau?

DR. PAU: I didn't hear from the sponsor, with regards to the screening process, how many patients were screened at the beginning that were found to be either dual/mixed or X4 tropic before you enrolled the individuals, the 700-something individuals?

DR. MAYER: Thank you for that question. Of the 1,730 patients who were screened for study 1026, 26 percent did not have an evaluable tropism result based on the original Trofile assay, and of the remaining 1,277 17 percent were excluded for a result indicating CXCR4-using virus.

DR. HENDRIX: Dr. Grant?

DR. GRANT: And of those who were originally excluded, wouldn't all of those have been picked up in the enhanced sensitivity assay?

DR. MAYER: Thank you, Dr. Grant. Yes, we believe, based on the data that we have seen from Monogram BioSciences, that those patients who were excluded based on the original Trofile assay for having CXCR4-using virus would have been picked up by the enhanced sensitivity Trofile assay.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: I saw in the FDA document, I believe, that 740 patients were actually randomized. Is that correct? Then actually I take it that a few people never took the drug in both treatment groups. Then, could you also just verify that your adverse event analyses which you showed were adverse events that occurred while taking treatment or just those in the short period after stopping?

DR. MAYER: Thank you, Dr. Neaton. Could I ask you to clarify the question? Sorry.

DR. NEATON: The first part was how many people were randomized to the study?

DR. MAYER: There were 740 patients who were

randomized to either the maraviroc BID or efavirenz treatment groups, and of those 740, 721 received at least one dose of therapy.

DR. NEATON: The original goal I saw was over 800, almost 900 patients. What was the reason for stopping short of that?

DR. MAYER: The original goal was actually to keep all three treatment groups, the maraviroc QD, maraviroc BID and efavirenz treatment groups, through to the end of the study but, as Dr. Heera presented earlier, one of the treatment groups, the maraviroc QD arm, was discontinued at the week-16 interim time point so that it didn't actually involve all the patients.

DR. NEATON: No, I understood that but I thought even in the other two treatment arms your goal was almost 900 patients. Did I misunderstand that?

DR. MAYER: No, that was not--

DR. NEATON: Your goal was about 740? What was your prespecified sample size?

DR. MAYER: I believe it was 357 per treatment group.

DR. NEATON: Okay. Then the other question was

about adverse events. Exactly what are we looking at here in terms of the 96-week period?

DR. MAYER: Adverse events on treatment or within one week post treatment, and for serious adverse events up to 28 days post treatment.

DR. HENDRIX: Mr. Marco?

MR. MARCO: Let's see, I believe on slide 32 where you have the breakdown based on baseline viral load less than 100,000 or more than 100,000, that is 48-week data. Do you have another slide that has it at 96 weeks, or can you give us those that stayed virologically suppressed?

DR. MAYER: Thank you for that question. If you can show slide E-129, please?

[Slide]

This is the slide showing the efficacy at 96 weeks with percentage of patients less than 50 copies/ml by screening viral load. You can see that for less than 100,000 copies/ml at screening the results were similar between maraviroc and efavirenz.

For the greater than 100,000 cohort the results were slightly greater on efavirenz than on maraviroc, and the reason for that switch between week 48 and week 96,

where at week 48 it looked like maraviroc might have been slightly better or they were similar, is, as Dr. Heera presented, related to the patients who had single viral loads above 50 copies/ml at week 96, half of whom were represented in this population.

So, it is the same explanation as Dr. Heera gave regarding the principal efficacy endpoint for week 96 and the TLOVR analysis at week 96.

DR. HENDRIX: Dr. Cargill?

DR. CARGILL: Thank you. A clarifying question on the demographics of the study participants. In the FDA provided materials it indicates that approximately 34 percent were black and, as you go on to read, they are predominantly southern hemisphere.

I recognize that the number for the Aother@ is small but my question is were these also still predominantly non-domestic populations, and what were those others because we don't have that data?

DR. MAYER: Can I ask you to clarify the question again?

DR. CARGILL: Certainly. The provided materials indicate in the demographics of the study that approximately

a third of the participants are black. The materials also go on to specify that the majority of them are southern hemisphere black. I am asking about the group that is Aother.@ I know it is small but I am asking who that population is and is it also primarily non-domestic?

DR. MAYER: They are predominantly mixed race and non-domestic.

DR. CARGILL: Thank you.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: I have two different sets of questions. The first has to do with statistical significance in the CD4 increase analysis and also in the grade 3 and 4 adverse events. You didn't show confidence intervals on your CD4 graph and there is no statistical testing shown about the difference in grade 3 and 4 AEs.

DR. MAYER: For the mean increases in CD4 count both at week 48 and at week 96, although Dr. Heera didn't show it, we did construct confidence intervals and the confidence intervals were to the right of 0 and didn't include 0 so they were statistically significant. For grade 3 and 4 adverse events we didn't formally conduct statistical analyses for those safety endpoints.

DR. ROLAND: And the second set of questions has to do with viral load greater than 50. You have discussed several times now that individuals at week 96 who failed on that definition having just a single viral load and on the subsequent viral load being greater than 50. So, a couple of questions about that.

First, did you retest the original samples that were greater than 50 to see whether on retesting the signal would be less than 50? The second is did you do that same sort of analysis at the week 48 failures in addition to the 96?

DR. MAYER: Thank you for the question. The answer to the first question is that we did not retest the HIV RNAs that were present at week 96--either at week 96 or at week 48.

DR. ROLAND: And with the week 48 failures did you do the same sort of analysis comparing maraviroc and efavirenz failures to see whether there was a single detectable viral load followed by an undetectable viral load, as you did at week 96?

DR. MAYER: If I can show slide E-68, please?

[Slide]

This is the TLOVR analysis at week 48 for less than 400 and less than 50 copies/ml. You can see that by the TLOVR analysis the original Trofile results actually were within the -10 lower bound and, obviously, with the enhanced assay reanalysis it continued to be within the -10 non-inferiority margin.

However, for the less than 50 copies/ml, unlike at week 96 where we actually were within -10 with the TLOVR analysis, we were just outside the -10 non-inferiority margin for the enhanced assay with an adjusted difference of -3.3 percent and a lower confidence bound of -10.4 percent.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: I have three specific questions. On slide 53 you gave us information about R5 virus and the percent that developed lamivudine resistance. I was wondering if you can walk us through your X4 virus and the percent that had lamivudine resistance.

DR. MAYER: Thank you for the question. I am going to hand this over to Dr. Mike Westby to address this in detail.

DR. WESTBY: Sorry, I didn't make it clear in my presentation. All patients with CXCR4-using virus at

failure also had lamivudine resistance.

DR. McGOVERN: My next question is in terms of the CD4 rise that was more significant in the maraviroc arm, did you analyze also CD4 percentages and if there were meaningful differences between the two arms?

DR. MAYER: There wasn't as great of a change in CD4 percentage because the kinetics in CD4 rise and CD8 rises were similar so overall the percentages didn't change as much as the absolute CD4 count.

DR. McGOVERN: And my last question, my knowledge of other non-inferiority studies is that they usually have two-sided confidence intervals and in this study the statistical analysis was designed to have a one-sided confidence interval and I was just wondering if you could comment on that decision.

DR. MAYER: Thanks again for the question. I would like to call up Dan Meyer who is the head of statistics for the anti-infective group at Pfizer.

DR. MEYER: Yes, to make a conclusion about non-inferiority you only really need to refer to the lower confidence limit so that is the only one we showed. It is the lower confidence limit of the 95 percent confidence

interval which could also be referred to as a 97.5 confidence bound.

DR. HENDRIX: Dr. Strader?

DR. STRADER: I am going back to the recruitment of patients. I understand the point that if you remove one of the arms the number of patients goes down. But you also mentioned that in the 300 mg QD dosing patients who responded were somehow included in the study. Is that correct? So, even though this dose was found to not have a good response, people who did respond were included in the study?

DR. MAYER: Thanks. Maybe we didn't make the presentation clear enough. The maraviroc QD arm was discontinued, which was a data safety monitoring board decision based on the interim analysis when approximately 200 patients were treated for 16 weeks, and the data that we showed you in safety and efficacy did not include those patients.

DR. HENDRIX: Dr. Van Dyke?

DR. VAN DYKE: Yes, I have a couple of questions about the retesting with the enhanced tropism assay. First of all, was it done on all of the subjects or just those

that were sensitive using the standard assay? And, the material that was tested, was it done on the original serum or plasma sample or was it using partially processed material?

DR. MAYER: Thanks. The enhanced assay reanalysis done by Monogram was done on patients who were randomized and received either maraviroc BID or efavirenz, and it was done on the PCR amplified product, not on the original plasma samples.

DR. VAN DYKE: And was it done on all of the subjects that were randomized or just those that were sensitive on the original assay?

DR. MAYER: It was done on all randomized subjects in the maraviroc BID and efavirenz treatment groups.

DR. HENDRIX: Can I ask you a follow-up question to that? During the study was the ESTA test done on all samples or only those that failed? You had many visits where you would have had samples stored perhaps but was the testing only done at the time of failure?

DR. MAYER: They were done on screening samples for those patients who either received maraviroc BID or efavirenz, but those were the only samples that were tested

with ESTA.

DR. HENDRIX: So, the CXR4 results at the time of failure was a different test?

DR. MAYER: Those were not retested with ESTA. Only the screening samples were retested with ESTA.

DR. HENDRIX: Dr. Grant?

DR. GRANT: Just to be clear, any participants who screened initially with evidence of a dual/mixed tropic or an X4 virus would never have been randomized in the original study, and the question really is were those people who screened out because of evidence of dual/mixed X4, were they retested using the more sensitive assay to confirm that the sensitive assay would have also excluded those participants?

DR. MAYER: Those subjects who screened out were not retested with ESTA, but based on data that we have and that we have seen from Monogram we believe that those patients would have still screened out with CXCR4-using virus with the more sensitive assay to detect low level X4 variants.

DR. HENDRIX: Dr. Pau?

DR. PAU: This is going back to the demographics a little bit. From the FDA material that we have it shows

that only 20 percent of the subjects were from the U.S., and from the data on the adverse events of patients who discontinued therapy with efavirenz it looks like, you know, obviously about 50 percent of the patients were from the southern hemisphere and probably a number of them were from Africa.

It seems that with differences in genetics and metabolism there could be for potential African patients having a longer half-life and probably higher drug concentration. Did you look at the discontinuation rate as grade 3/4 events among efavirenz or maraviroc patients and whether there was any difference in adverse events by continent or by geographical area?

Along the same lines, it looks like there are a lot of TB patients in the efavirenz arm. Is there a different distribution geographically and where those individuals came from?

DR. MAYER: We did look at the adverse event profile in different geographic locations and there was no difference by geographic location or by race in terms of the overall adverse event profile of maraviroc versus efavirenz.

DR. HENDRIX: Dr. Veltri?

DR. VELTRI: I have two questions. One relates to the interim analysis which occurred, I believe, at 16 weeks in about 200 patients. With the QD dose that was dropped did you go back and re-assay those patients with the high sensitivity analysis to see perhaps if there was more XR4 in that population, or was it simply a PK possibility even though it was stopped by the DSMB?

The second question relates to this. Was the last observation carried forward analysis, I would imagine, at 48 weeks? Did you do a completers analysis to try to balance the discontinuations with the actual virology?

DR. MAYER: Thanks for that question. Can I have slide E-21, please?

[Slide]

To answer your question, we did actually go back and look at what would have happened had we used the enhanced assay reanalysis. On the left, it shows you the QD results with the original Trofile assay which shows that for the less than 400 endpoint--which was one of our co-primary endpoints for making a decision about the QD and the BID arm versus efavirenz at the interim analysis at 16 weeksB-only 78 percent of patients on the QD arm versus 88.4 percent on

efavirenz achieved a viral load at week 16 of less than 400, and our lower confidence bound was -20. So, at -25.9 that fell outside of the lower confidence bound and that is the reason why the DSMB discontinued the QD arm.

However, we looked at the enhanced assay reanalyses and went back and did the same analysis and it shows that the differences are narrower even for the QD arm, at 82.1 versus 86.2, with an adjusted difference of -4 and a lower confidence bound of -19. So, in all likelihood, had we had the original assay the QD arm probably would not have been discontinued. We don't know for sure.

In terms of the second question, this was a non-completer equals failure analysis. This wasn't the last observation carried forward for the virologic endpoint. So, this was a non-completer equals failure analysis.

DR. HENDRIX: Miss Swan?

MS. SWAN: Can you show us a breakout of the baseline CD4 strata?

DR. MAYER: Thanks for the question. I would like to call up slide E-136, please.

[Slide]

This shows actually efficacy by baseline CD4

strata in terms of the percentage of patients that achieved less than 50 copies/ml at week 48. Obviously, we looked at this because we wanted to look at the lowest CD4 strata and there were 37 patients in this analysis with CD4 counts of less than 100. The results showed that the efficacy of maraviroc was a bit better than with efavirenz in that strata, and similar efficacy results in the other strata of, you know, 100-200, 201-350 and greater than 350.

DR. HENDRIX: Dr. Hagedorn?

DR. HAGEDORN: Yes, I have a question regarding the analysis of hepatic adverse events. What percentage of the patients were on anti-tuberculous agents, and what were those agents? Also, were patients allowed to take acetaminophen? If so, what dose limitations might there have been?

DR. MAYER: I think in terms of question number oneB-thank you for the questionB-we had no patients on anti-tuberculous therapy while they were receiving maraviroc.

I think we probably need to get back to you after the break on the percentage of patients that received acetaminophen in treatment groups. We have the information, I just don't have the answer for you right now. But if it

is acceptable to the chair, I can get back to you on the acetaminophen question after the break. Thank you.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Can you clarify for me, when using the old Trofile you went back and compared the Trofile screening which had to be R5 and then in the failures they went back and looked at the baseline one as well and found that some had changed from screening at baseline?

That was part of what you pointed out as an interesting component. When people failed in the ESTA analysis with X4 virus did you go back and use the ESTA analysis on their baseline test to see if they had a discrepancy between screening and baseline that had likewise been found in the prior analysis?

Is that clear? There is a screening test and a baseline test. All the ESTA data you show us is on the screening test. We don't get to know how many people who screened ESTA-negative might have been ESTA-positive at baseline. The issue is how many are missed by the initial screening ESTA test. If you did two would you have gotten rid of all of the X4 failures because they really were ESTA-positive on retest? So, did you, in the failures with X4,

look at the baseline ESTA test, and how many were positive if you did that?

DR. MAYER: Thank you for the question. I understand. We actually, unfortunately, did not look at the baseline samples, but the reason we concentrated on the screening samples was really to replicate what would happen in clinical practice, consistent with the guidelines. Basically that if you are considering using maraviroc you should obtain one tropism test. So, we concentrated on the screening tropism test which would have been that test that got patients into the trial, and did not look at ESTA in the baseline samples.

DR. HENDRIX: Dr. Cargill?

DR. CARGILL: Thank you. I would like to return to the hepatic adverse events question. As approximately 30 percent, according to the materials, of your population was female do you have information on concomitant exogenous hormones, especially estrogens?

DR. MAYER: Thanks for the question. I think we will also have to request that we get back to you after the break not only on concomitant use of acetaminophen but also concomitant use of exogenous hormone therapy, if that is

acceptable. Thanks.

DR. HENDRIX: Yes, Dr. Grant has an addition to your list.

DR. GRANT: Could you also tell us how many were taking Viagra at some point during the trial?

DR. MAYER: I think we can get that information as well. Thank you.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: In the original materials I was trying to figure out, since this is a blinded study, were the efavirenz arm patients taking a placebo drug so that they weren't taking meds twice daily?

DR. MAYER: Thank you, Dr. McGovern. This was a double-blind, double-dummy strategy so patients were taking dummy maraviroc placebo pills twice daily. The efavirenz patients were taking maraviroc BID placebo drugs.

DR. HENDRIX: Dr. Pau?

DR. PAU: In the conclusion there were two statements that were made. One is that it is safe to be used during pregnancy because it is a pregnancy category B. Do you have true data on patients who were pregnant to make that statement?

Secondly, you also indicated that it is safe to use together with TB treatment. As far as I know, rifampin significantly reduced the level of maraviroc, and at least in the current package insert it is recommended to double the dose to 600 mg BID Do you have safety data and efficacy data that while a patient is on a rifampin-based regimen together with maraviroc to make the statement that it is safe and effective to use it for TB patients?

DR. MAYER: Thank you for that question. Can I please call up slide S-110?

[Slide]

So, we do have pregnancy data in the 1026 study. There were seven cases of pregnancy in the maraviroc BID group. Three reached full term and had normal babies. Two patients had induced abortions and two were lost to follow-up. There were ten cases of pregnancy in the efavirenz group. Two reached full term and had normal babies. Four had induced abortion, two spontaneous abortions, one still birth and one was lost to follow-up.

And, there has been no evidence of fetal malformation in either treatment arm or, to our knowledge, on maraviroc. We are participating in a pregnancy registry

and we have not seen any evidence of teratogenicity on maraviroc.

In terms of tuberculosis, as I mentioned before, we didn't have any patients in the study in the maraviroc BID and efavirenz treatment groups who actually were being treated for TB while on those medications. But we did conduct a drug-drug interaction study with rifampin and the recommendations that are currently in the package insert for maraviroc are to double the dose of maraviroc, when given in combination with rifampin, to 600 mg BID So, it can be used with rifampin.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: We will come back, I am certain, in a lot more detail in Dr. Proestel's kind of key question, at least in my mind, about the endpoint and the problem it creates in a study like this.

But one thing that would be helpful, before we get into that, is I noticed in the FDA briefing and your briefing the reasons for discontinuation didn't line up. So, I guess one question is when patients discontinued study treatment did the investigator have to fill out a case report form and specifically indicate the reason why they

discontinued? And, is that the basis of some data that we will ultimately see?

DR. MAYER: Yes, all of the reasons for discontinuation were based on the primary investigator's decision as to why the patient discontinued.

DR. NEATON: So, I notice that they differ. We can come back to that but I gather, based on both what you reported and what the FDA reported, the investigator checked one reason because the numbers added up and there was only one reason given. Is that correct?

DR. HENDRIX: Miss Swan?

MS. SWAN: Can you tell us how many people in each arm had less than 50 CD4 cells at study entry and less than 100?

DR. HENDRIX: You can bring your response back after the break. Do you have a couple more questions, Mr. Marco?

MR. MARCO: At least from the patients that you have data on with the enhanced Trofile assay, it seems like there are approximately 246 who have HIV exposure classified as men who have sex with men, and 317 heterosexual contacts. Can you tell me is there a difference in those two

populations as far as country of origin?

DR. MAYER: Yes, thank you for that. The SMs were predominantly in the northern hemisphere and those who acquired HIV through heterosexual contact were predominantly in the southern hemisphere, or over-represented in the southern hemisphere.

MR. MARCO: Thank you.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Getting back to Dr. Pau's question about use in pregnancy, one of your opening slides suggested that pregnancy was an important consideration and here one of your closing slides suggested that pregnancy was a use that you will be targeting. Do you have any data on pharmacokinetics of maraviroc in pregnant women, understanding that pregnant women are a special challenge for the drug kinetics?

DR. MAYER: No, we don't.

DR. HENDRIX: Let me ask you a PK follow-up question on that. How was the C-average calculated? I am guessing but if you could tell me for sure.

DR. MAYER: I am going to bring up Lynn McFadyen to address this question, who is the pharmacometrics lead for

maraviroc. But before she steps up to the microphone I can tell you, getting back to your CD4 question, there are ten patients with CD4 counts of less than 50 and 23 patients with CD4 counts of less than 100. Lynn, I will hand over the question on C-average to you.

DR. McFADYEN: Thank you. If I can have slide CP-23, please?

[Slide]

So, the C-average was calculated from PK taken on 10 occasions over the 48 weeks. So, at week 2 they had 2 samples taken. At week 48 they had 2 samples taken and on all the other visits only 1 sample. This was then used in a population pharmacokinetic modeling and you can see the results for 2 subjects, 2 representative subjects on the slide, with the person on the left-hand side showing a large number of samples clustered quite close together, and then on the right-hand side a subject who withdrew early, with less samples and the PK is really all over the place, including 2 BLQ samples right at the bottom.

So, you can clearly see that one would have a low C-average and the other much higher C-average. The PK used patient-reported dosing and that is how we calculated it.

DR. HENDRIX: So, the C-average calculations are from the fitted data or from the actual data?

DR. McFADYEN: Fitted data. Thank you.

DR. HENDRIX: Dr. Pau?

DR. PAU: I just want to have another follow-up question about the pregnancy issue. By the study protocol would an individual who became pregnant and was found to be pregnant be discontinued from the study arm? I would assume that is the case. If so, do you have the duration of exposure for those individuals, as well as the treatment outcome, or actually the HIV-positivity of those newborns?

If that is the case, also would they be indicated in the discontinuation in your protocol, that the reason for discontinuation is because of pregnancy? Because there is quite a large number of patients who become pregnant during a study protocol which is larger than what we usually see in the treatment-naive trial.

DR. MAYER: Thank you for that. As I mentioned before, there were 17 pregnancies in study 1026. These were all, obviously, in HIV-infected women, predominantly in South Africa, and they were discontinued as per study protocol. I think I am going to have to request again to

get back to you on the duration of exposure in those women.

DR. HENDRIX: Let me ask if there are any last questions for clarification from the panel. If not, we will take a break until 10:10 a.m. I will remind the panel members that there will be no discussion of the meeting topic during the break amongst ourselves or with any member of the audience. So, see you back in 15. Thank you.

[Brief recess]

DR. HENDRIX: I would like to call the meeting back to order. There were a few questions that the sponsor was going to look up the answers to during the break and present to us, so I will go ahead and give them an opportunity now if they want to present those answers. There was a question about acetaminophen, estrogens and Viagra, and also about the duration of exposure in pregnancy.

DR. MAYER: In terms of acetaminophen, the use of acetaminophen was in 23.3 percent of efavirenz-treated subjects and 25.3 percent of maraviroc-treated subjects through week 96.

For PB-5 inhibitors, not just sildenafil but all ED drugs, it was 13 on efavirenz and 11 on maraviroc.

We are still working on the external hormonal

therapy but we will have that shortly. For the pregnancy cases on maraviroc, all of those were diagnosed in the first trimester of pregnancy so all of them had similar exposure through the first trimester of pregnancy. And, we have information on three babies and two of three of them were HIV-negative on maraviroc.

In terms of pregnancy, just to clarify, when I showed the slide of potential patient populations where maraviroc could be used we were just stating that this is a potential option for those women, and nothing more than that. We have preclinical data. We have embryo/fetal tox data showing no evidence of teratogenicity, and we are continuing to participate in the pregnancy registry and so far, again, to this point there has been no evidence of teratogenicity.

DR. HENDRIX: Thank you. At this point we will proceed with the presentation from the FDA. I will remind the gallery againB-first of all, thank you, all of you that are in the gallery, if that is what we call it, the galleryB-the audience-Bfor showing up and being here. Your participation will be only at the specific request of the panel. So, with that in mind, I will go ahead and turn it

over to FDA. Thank you.

FDA Presentation

DR. MISHRA: Good morning.

[Slide]

I am Poonam Mishra. I am a medical officer in the Division of Antiviral Products at FDA.

[Slide]

Today I will be presenting data on behalf of the FDA maraviroc review team. My presentation today will include an introduction and brief regulatory background. I will then go over the clinical efficacy results based on FDA analysis of the data. I will discuss clinical virology and pharmacology issues pertinent to the treatment-naive indication for maraviroc. At the end I will go over the clinical safety results for the treatment-naive population.

[Slide]

Just to go briefly go over the regulatory background, maraviroc is a selective, slowly reversible, small molecule CCR5 co-receptor antagonist which inhibits entry of CCR5 tropic HIV-1 into cells.

It was approved in August of 2007 for treatment-experienced patients infected with only CCR5 tropic HIV-1.

This was an accelerated approval based on 24-week data. Later on maraviroc received traditional approval in November of 2008. This was based on 48-week data from two phase 3 studies, 1027 and 1028.

[Slide]

The applicant has submitted data from study 1026 in support of a new indication for the use of maraviroc in treatment-naive adult patients infected with only CCR5 tropic HIV-1. The initial plan was to submit week 48 data but the applicant awaited week 96 data before filing due to concern about the high rate of virologic failure seen with maraviroc.

[Slide]

I will briefly go over the study design. Study 1026 was a 96-week multinational, double-blind, randomized 1:1:1, non-inferiority phase 2b/3 hybrid trial to compare the safety and efficacy of maraviroc at two different doses versus efavirenz, each in combination with zidovudine and lamivudine.

Major eligibility criteria for enrollment were male or female subjects greater than or equal to 16 years of age; infected with CCR5 tropic only HIV-1 with a viral load

greater than or equal to 2,000 copies/ml. They could not have previously received any antiretroviral therapy for more than 14 days, and there should be no evidence of active or recent opportunistic infection or a suspected primary HIV-1 infection.

[Slide]

Primary efficacy endpoints were defined as the percentage of subjects with HIV-1 RNA undetectable by the standard of less than 400 copies/ml and ultra sensitive methods which is less than 50 copies/ml using a one-sided 97.5 percent confidence interval.

This was designed as a non-inferiority trial, and if the lower bound of the confidence interval of the difference in treatment effect was -10 percent and delta of -0.1, non-inferiority between maraviroc 300 mg BID and efavirenz 600 mg QD was to be concluded.

Subsequent to the analysis of the week-48 data, Monogram Biosciences released an enhanced version of the Trofile assay. This is the only commercially available assay in practice now. The applicant retested all the screening samples for CCR5 tropism using this new assay and has provided these analyses in the current submission. All

endpoints at week 96 were considered secondary.

[Slide]

A prespecified interim analysis was done at 16 weeks and, based on the recommendations from the data safety monitoring board, the maraviroc 300 mg QD arm was discontinued as it failed to meet the prespecified criteria for establishing non-inferiority to efavirenz.

The maraviroc 300 mg QD arm was dropped and randomization was changed to 1:1. As the maraviroc QD arm was discontinued and the dosing requested for approval in treatment-naive patients is twice daily, the majority of analyses to be presented will be for the maraviroc BID arm.

[Slide]

Drop-arm adjustment was done and 205 subjects finished 16 weeks and were included in the interim analysis. Total sample size was reduced to 891 instead of 1,071. A total of 360 subjects received maraviroc 300 mg BID and 361 received efavirenz 600 mg QD.

For a three-arm trial, one-sided 98.75 percent lower bond should be used with Bonferroni adjustment. If a two-arm trial, one sided 97.5 percent lower bound would be acceptable.

[Slide]

Now I will discuss the clinical efficacy results based on our analysis.

[Slide]

This table summarizes some of the demographics and baseline characteristics of subjects from study 1026. As you can see, most of these demographics and baseline characteristics were well balanced between the two treatment groups. The majority of subjects were male, 71 percent, and Caucasian, 56 percent, although there was a greater representation of blacks, 36 percent, in this trial than in the treatment-experienced trials. There was a smaller proportion of subjects infected with HIV clade B in study 1026 compared with the treatment-experienced trials where it was 94 percent respectively.

[Slide]

I will discuss the subject disposition at week 48 since week 48 was the primary efficacy endpoint of the study. The final full analysis set population was 721. There were 360 subjects in the maraviroc BID arm and 361 subjects in the efavirenz arm. Those who completed study were similar in both groups. A similar number of subjects

discontinued study treatments by week 48.

Of note, 12 percent of subjects in the maraviroc group versus 4 percent in the efavirenz arm discontinued due to lack of efficacy. More subjects in the efavirenz arm compared to the maraviroc arm discontinued due to adverse events at week 8. So, when you look at the combined related adverse events and unrelated adverse events, 14 percent in the efavirenz arm compared to 4 percent in the maraviroc arm discontinued due to adverse events at week 48. A similar trend was maintained at week 96.

[Slide]

Now I will discuss the primary efficacy results. This table provides the FDA analysis of the virologic outcomes at weeks 48 and 96, using the original assay at the top and using the enhanced assay at the bottom of the table. The primary efficacy endpoint of the difference in percentage of subjects with undetectable viral load at week 48 by the standard, less than 400 copies/ml using the original assay, was met. You can see this was within the non-inferiority margin. But it failed to meet the primary efficacy endpoint of percentage of subjects with viral load less than 50 copies/ml at week 48.

Using the reanalysis results performed based on the enhanced assay, the non-inferiority margin was met for both less than 400 and less than 50 endpoints at week 48, and it was met for less than 400 copies/ml at week 96. However, it failed to meet the less than 50 copies/ml endpoint at week 96 using the enhanced assay.

[Slide]

We did some subgroup analyses based on region and HIV subtype at week 48 using less than 50 copies/ml and using the enhanced assay. Subjects in the United States appeared to have improved neurological outcomes with maraviroc BID compared to efavirenz, 76 percent in the maraviroc arm compared to 62 percent in the efavirenz arm.

Although these numbers are small, and we have to keep that in mind, a trend in favor of maraviroc BID was noted for subjects in the United States, as well as for those infected with clade B.

[Slide]

Just to summarize the efficacy results, the primary efficacy endpoint difference in percentage of subjects with undetectable viral load at week 48 by the standard, less than 400 copies/ml, method using the original

assay was met but failed to meet the primary efficacy endpoint of percentage of subjects with viral load less than 50 copies/ml.

Using the reanalysis results the non-inferiority margin was met for less than 400 copies/ml and less than 50 copies/ml at week 48 and for less than 400 copies at week 96. It failed to meet the non-inferiority margin for less than 50 copies/ml at week 96 endpoint. The results were 85.8 percent and 62.7 percent undetectable for the maraviroc and efavirenz arms respectively. A numerical difference in favor of maraviroc BID was noted for the subjects in the U.S. and for those infected with HIV clade B.

[Slide]

Now I will discuss the clinical virology.

[Slide]

Study 1026 used the original Trofile assay, which was the only available tropism test at the onset of the pivotal maraviroc studies. In the treatment-naive study the results using the original tropism assay for screening showed that 26 percent of the virologic failures failed the CCR5 tropic virus, similar to the efavirenz arm. So, this percentage which failed at screening with the original assay

was comparable between the two arms.

Virologic failure with dual/mixed or CXCR4 tropic virus at failure was observed in 21 percent in the maraviroc arm compared to 3 percent in the efavirenz arm. So, those who failed with CXCR4 tropic are 21 compared to 3 in the efavirenz arm.

Note that 50 percent of the virologic failures were below the level of quantification of the tropism assay, or non-reportable, and did not have a tropism test. This is shown at the bottom of the slide. Outgrowth of X4-using virus not detected at screening for maraviroc treatment is a prominent reason for maraviroc virologic failure in this trial, as was seen in the maraviroc treatment-experience trials.

[Slide]

In June, 2008 Trofile with enhanced sensitivity was released for clinical use based on data demonstrating increased sensitivity of the assay for the detection of chemokine receptor 4, CXCR4 tropic virus. Therefore, screening tropisms were reevaluated with the enhanced sensitivity tropism assay and 96-week data were reanalyzed based on the new tropism results.

When using the ES tropism assay results for screening 14 percent of the subjects in the maraviroc arm were removed from the analysis with dual/mixed tropic virus and 16 percent of the subjects in the efavirenz arm were removed from the analysis with dual/mixed tropic virus.

[Slide]

Of the 49 subjects in the maraviroc arm and 58 in the efavirenz arm screened out of the analysis because they had dual/mixed tropic virus, in the ES tropism assay 43 percent were virologic failures in the maraviroc arm compared to 12 percent in the efavirenz arm. More virologic failures were screened out from the maraviroc arm, thus suggesting screening with the more sensitive tropism assay may reduce the number of maraviroc virologic failures.

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Following removal of those that screened dual/mixed by the enhanced assay and reevaluation of the censored ES treated data, there were 32 percent virologic failures in the maraviroc arm, down from 35 percent, compared to 24 percent in the efavirenz arm. There were still more maraviroc failures than efavirenz failures.

[Slide]

A similar percent of virologic failures were R5 tropic at failure in the maraviroc arm, 34 percent compared to 28 percent in the efavirenz arm.

[Slide]

Fourteen percent of the maraviroc failures were X4 or dual/mixed tropic at failure compared to 3 percent in the efavirenz arm. Note that the original tropism assay results were still used for determining tropism at failure. So, greater than 50 percent of the virologic failures were below the level of quantification and were non-reportable.

[Slide]

Fewer virologic failures were dual/mixed or X4 failures using the ES tropism assay screening results, 14 percent down from 21 percent with the original assay results and no change in the efavirenz arm was seen.

[Slide]

Now I will go over some of the reasons for virologic failures.

[Slide]

There are a number of reasons for virologic failure on maraviroc. Outgrowth of undetected CXCR4-using virus; viruses could be dual/mixed or CXCR4 tropic at

failure; maraviroc phenotypic resistance; CCR5 tropic virus at failure; background therapy resistance, lamivudine or zidovudine resistance; and low exposure to maraviroc.

[Slide]

As we just showed, 14 percent of maraviroc virologic failures failed with X4 or dual/mixed tropic virus using the screening results of the ES tropism assay.

[Slide]

Almost all, 11 out of 12 and that is 92 percent, were X4 or dual/mixed tropic maraviroc failures were resistant to background therapy, and 92 percent developed lamivudine resistance and 33 percent developed zidovudine resistance.

[Slide]

Looking at virologic failures who failed with CCR5 tropic virus, of the 29 in the maraviroc arm 7 had phenotypic evidence of maraviroc resistance with less than 95 percent maximal percentage inhibition of maraviroc use. Seventy-three percent of the efavirenz failures had phenotypic evidence of efavirenz resistance.

[Slide]

Sixty-two percent of these virologic failures had

resistance to a drug in the background therapy compared to 36 percent in the efavirenz arm. So, more were maraviroc failures with a drug in the background therapy.

[Slide]

To summarize clinical virologic results, re-screening with the enhanced sensitivity tropism assay reduced the number of maraviroc virologic failures with dual/mixed or CXCR4 tropic virus at failure. However, there were still 32 percent virologic failures in the maraviroc arm compared to 24 percent in the efavirenz arm.

Regardless of tropism at failure, subjects failing maraviroc lose an additional drug in their background therapy significantly more than those subjects failing on efavirenz. Seventy-one percent had genotypically detectable resistance to at least one drug in the background therapy compared to 33 percent in the efavirenz arm.

[Slide]

We looked at some of the reasons for low exposure to maraviroc, and based on exposure response analysis of data from study 1026 a C-average value of 65 ng/ml was determined as a reasonable pharmacokinetic cut-off to predict whether a subject has a low or high probability of

success on maraviroc.

Out of the 9 subjects who failed with CCR5 tropic virus without detectable resistance to maraviroc or background therapy 5, which is 56 percent, had a C-average less than 65 ng/ml. Therefore, low exposure to maraviroc may explain the failure of some of these subjects on maraviroc treatment.

[Slide]

A clear relationship with maraviroc exposure and probability of virologic response was observed. On this slide maraviroc average concentration is shown on the X axis and the probability of being a responder is shown on the Y axis.

As average maraviroc concentration increases the probability of virologic response increases and approaches an approximate maximum at maraviroc average concentration greater than 65 ng/ml, which is shown on this graph.

[Slide]

Ten percent of the subjects in this study had maraviroc C-average below 65 ng/ml. Demographic factors such as age, weight and race do not explain the occurrence of C-average values less than 65 ng/ml. There was some

evidence of possible missed doses in 14 of the 31 subjects who had PK concentrations below the limit of quantification. Based on phase 2 data, concentrations this low are likely in subjects who are non-compliant.

We examined the benefit of therapeutic drug monitoring in these 31 subjects by seeing what would happen if we doubled their dose. The results are displayed in the table. In those 31 subjects the probability of virologic success is increased from 42 percent to 60 percent if we double the original dose. This is simulated data. In the study population as a whole the probability would increase from 72 percent to 74 percent.

[Slide]

Now I am going to go over the clinical safety results based on week-96 data. There were 500-patient years of exposure to maraviroc in the treatment-naive population in this study during the double-blind period.

[Slide]

There was a total of 12 deaths reported during the double-blind period, 6 in each treatment group. There was no clustering of death causes seen and causes of death were consistent with the population being studied and were mostly

related to underlying HIV infection and due to complications of AIDS.

[Slide]

Due to the possibility that inhibition of CCR5 receptor could result in increased immune surveillance there has been concern regarding the carcinogenic potential of maraviroc.

[Slide]

There was a total of 18 malignancies reported in 16 subjects. Based on these results, there was no increased frequency of malignancies observed in association with maraviroc use.

[Slide]

Hepatotoxicity has been of concern during the maraviroc drug development. A potentially drug-related case of hepatotoxicity resulting in liver transplant occurred in this study in the maraviroc QD treatment arm. This case was previously reviewed at the time of initial approval and alternative explanations for liver disease were present in this subject. There was evidence of worsening liver inflammation prior to maraviroc use in this subject.

There was a healthy volunteer case in a phase 1

study who had rash, fever and eosinophilia, and subsequently was found to have a concurrent group A streptococcal infection. This case was also reviewed at the time of initial approval, and it led to a hepatotoxicity boxed warning in the maraviroc label.

In study 1026 there was one subject per group who met the biochemical definition for Hy's law. Both of these subjects had identifiable alternative causes, which are listed below--biliary sludge, pancreatitis, alcoholism and hepatitis C.

[Slide]

For this study the liver-related eligibility criteria were that subjects were excluded if they had elevated baseline transaminases, greater than 3 times the upper limit of normal, or total bilirubin greater than 2 times the upper limit of normal. Hepatitis B and hepatitis C co-infected subjects were included in the study although the numbers are small. Subjects with hepatic cirrhosis were excluded from the study.

[Slide]

This is a table showing all-causality hepatic adverse events occurring in the double-blind period. There

was a total of 21 liver-related AEs reported in 19 subjects. Six subjects received 6 AEs in the maraviroc arm and there were 13 subjects who experienced 15 adverse events in the efavirenz arm. There was no increase noted in all-causality hepatobiliary adverse events or serious adverse events in the maraviroc group. Discontinuations related to hepatic adverse events were lower in both groups and there were no fatal outcomes reported related to hepatic events.

[Slide]

As maraviroc blocks a receptor used by immune cells there has been concern regarding potential increased risk of infections due to exposure to this drug. No overall increase in infections was observed in association with maraviroc during this study.

[Slide]

A similar percentage of subjects, 62 percent, reported infections in each treatment arm. Unlike the phase 3 trials in treatment-experienced subjects, no increase in incidence of upper respiratory tract infection or influenza was noted with maraviroc use.

[Slide]

There have been some other safety concerns

regarding the maraviroc development program. No overall increase in category C AIDS-defining illness was observed in the maraviroc group.

And, assessment of cardiovascular events in the maraviroc arms in treatment-experience trials led to some cardiovascular safety concerns with maraviroc. There were 11 subjects in the maraviroc arms in the treatment-experience trials with cardiac ischemic events during the double-blind period of studies 1027 and 1028 and no such events in the placebo arm.

This has raised concern that maraviroc could cause cardiac ischemia. However, in study 1026 all-causality cardiac adverse events reported under cardiac disorders were comparable in both groups, and they are listed here.

Adverse events consistent with postural hypertension were assessed as this was the dose-limiting AE observed during the maraviroc clinical development. As you can see, all-causality postural events were higher in the efavirenz arm, 36.8 percent, compared to the maraviroc arm, 16.6 percent.

[Slide]

This table shows all-cause common adverse events

which were reported in greater than 10 percent of subjects in any treatment group. Adverse events such as dizziness, rash and abnormal dreams were seen at a higher frequency in the efavirenz group.

[Slide]

To summarize the safety results, maraviroc appeared to be well-tolerated in this phase 3 study in treatment-naive HIV-1 infected subjects.

No clinically significant imbalance was observed in mortality rate, malignancy or AIDS-defining illnesses. In addition analyses of hepatic and PK-related AEs did not detect a safety signal associated with maraviroc.

[Slide]

To summarize the presentation, the primary endpoint at week 48 was met by HIV-1 RNA less than 400 copies/ml using the original assay but failed to meet the HIV-1 RNA less than 50 copies/ml endpoint.

Using the reanalyses, the non-inferiority margin was met at week 48 by HIV-1 RNA less than 400 copies and less than 50 copies, and it met the HIV-1 RNA less than 400 copies endpoint at week 96.

There were more discontinuations due to virologic

failures in the maraviroc arm compared to more discontinuations due to adverse events in the efavirenz arm. More maraviroc failures developed resistance to background drugs than efavirenz failures. Subjects with maraviroc C-average value greater than 65 ng/ml have a higher probability of virologic success. No new safety signals are identified with maraviroc use.

[Slide]

I would like to acknowledge the contributions of the entire review team and contributions of the team members, Dr. Naeger, Dr. Krudys and Dr. Zeng who have provided the slides from their respective disciplines. Thank you very much.

Clarifying Questions for FDA

DR. HENDRIX: Thank you. At this point we will take clarifying questions from the committee for the FDA's presentation. Dr. Van Dyke?

DR. VAN DYKE: Regarding the drug exposure response association you showed, did you look at either weight or body surface area to see whether that could explain some of the low drug exposures, people with either high body surface area or heavier patients? Did you look at milligrams/kilo

for instance?

DR. MISHRA: I will defer this question to my pharmacology colleagues.

DR. KRUDYS: Kevin Krudys, pharmacometrics reviewer. We did look at the weight. So, we did look at the weight and we tried to see if that would affect clearance or the exposure and we found that it did not explain changes in exposure for maraviroc.

DR. HENDRIX: Dr. Dixon?

DR. DIXON: Actually I have a question that I could have raised in the previous presentation but I will raise it now. Could I just get an idea of the distribution of the study population among the four strata for the randomization? If it is not handy to give the actual numbers in each of the four strata, could I just get some indication of whether any of the strata were nearly empty or very minimally represented?

The related question has to do with the primary analyses being adjusted for the randomization strata. So, sort of a related question is whether the same sort of adjustments were used in the sponsor's analysis when the comparisons were adjusted for the randomization strata.

DR. MISHRA: Dr. Wen Zeng from statistics will answer that question.

DR. ZENG: This is Wen Zeng, staff reviewer from FDA.

The four strata numbers are well-balanced. I checked it. There are no empty cells.

And I think that probably the reason you asked the question is because the rates are the same but the lower bound accompanying them is a little bit different. I think it is because the methods are a little different.

In the sponsor's method, they used the weighted--they used the inverse of the virus as a weight to do the adjustment. But we used the number of the subjects in each strata as a way to do the adjustment. That is a subtle difference, but the conclusions are the same.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: This is partially clarification but it may get into more than that so just cut me off if it does. If we could have slide 11 up?

[Slide]

I view this as a very important slide in understanding what is going on with this composite outcome.

I will ask a question so that I understand it. So, basically, when you go to slide 12, perhaps you can flip to thatB-

[Slide]

B-when you go to slide 12 you are using the completers in this slide to determine whether they have a viral load less than 400 at 48 weeks. So, if you go back a slide--

[Slide]

Just in terms of getting the numerator, it is 263 people whose viral load is analyzed at 48 weeks to determine if it is less than 400. Is that correct?

DR. PROESTEL: That is not correct. The statisticians may want to weigh in on this but slide 12 includes everyone--

DR. NEATON: No, I know the percent includes everyone. I am talking about the numerator. So, you measured the viral load at 48 weeks. As I understood it, there were 263 people and among those 263 peopleB-the numbers are not there on this particular slide, but in 254 of those 263 in whom you measured the viral load it was less than 400. I am not talking about the denominator; I am

talking about the numerator.

So, if you think of it that way, the 263 minus the 254 is 9 people on whom you measured the viral load that was above 400. Then, in addition, you have 43 people that were discontinued for lack of efficacy. So, my counting gives me 52 people for whom there was evidence in the maraviroc arm for kind of lack of virologic efficacy as compared to the efavirenz arm where the corresponding numbers are 21. So, you know, it is a 2.5-fold difference in terms of number of people that are kind of failing virologically during the first 48 weeks of the study.

I mention that because I think the problem, if you go back to the next slide--

[Slide]

B-this endpoint, which is the denominator, the non-responders, so to speak, is a gemish of people that are failing for adverse events, who are lost to follow-up, and who had failed virologically. So, to be kind of blunt, it is kind of a composite of sloppiness, safety and efficacy. So, if I want to look at virologic efficacy I don't think this is a very good outcome in this study. But I want to verify that I am understanding your computations correctly.

DR. PROESTEL: I believe, certainly, the point that you are making we agree with. The numbers were running by pretty quickly there. But certainly the point that you are making we agree with. This is a modified ITT analysis and, certainly, that is the one that is generally used but, depending on how a trial unfolds, you know, there can be complicated reasons for why you would have overall similar results.

DR. NEATON: So, if we go back one slide I think it would be helpful for the committee to see this slide at week 96, as well as kind of the corresponding numbers. That is in your report. I mean, there you get a similar picture in terms of the percentage of people that are failing virologically. I mean, it is important to understand the safety as well as the efficacy of these drugs, and I think you have to do a little disentangling here to get at that because of the reasons for the discontinuation being so varied.

DR. HENDRIX: Dr. Pau? No? Dr. Grant

DR. GRANT: Just to make sure I understand slide 22, it looked like 14 percent of virologic failures in the maraviroc arm were found to have a dual/mixed or CXCR4 virus

using the ES assay but 21 percent were found to have X4 virus using the original assay. Am I understanding that correctly, that the original assay picked up more X4 viruses than the ES assay in this analysis?

DR. NAEGER: No, this is the ones that were screened. This is only screening. So, if you use the ES screening assay, then you only have 14 percent that failed with dual/mixed or X4 virus. But when you screen with the original assay you have 21 percent that failed with X4, dual/mixed.

DR. GRANT: I get it, okay.

DR. HENDRIX: Just a quick reminder to identify yourself.

DR. NAEGER: I am Dr. Naeger.

DR. GRANT: And a more general question, have the performance characteristics of the Trofile assay been reviewed by the FDA?

DR. NAEGER: Yes. Our Division is not responsible for that but I have reviewed it for this application and as well had a consult with the appropriate division.

DR. GRANT: Can I get just one more question about the safety? I would like to hear more about the case that

went to liver transplant. What concomitant etiologies were present, and was the overall pattern one of cholestatic hepatitis? You know, it is only a single case, I appreciate that, but when you have liver failure you have to know the details. You know, it was a few cases that stopped development of another drug in the same class.

DR. MISHRA: This was a female subject and she was on anti-tubercular drugs prior to starting maraviroc. Her baseline liver functions were elevated prior to starting maraviroc. She also had hepatitis C virus and she had a high baseline viral load as well for hepatitis C. So, these were confounding factors. And, this is the maraviroc open arm subject.

DR. GRANT: So, receiving anti-tubercular medications for active disease, was that an exclusion criteria for this study? How did she get into this study? She was receiving therapy for tuberculosis. I mean, I am just curious. Was there an exclusion for active and serious concomitant infectious disease?

DR. PROESTEL: I think Pfizer can certainly weigh in. I thought at the time it was allowed and subsequent to this event it was excluded. Following this event there were

no more patients allowed.

DR. MAYER: Yes, I can clarify, if it is okay for us to weigh in. Can I have slide S-27, please?

[Slide]

This actually shows you the timeline for this case which occurred four years ago. This was a woman, a Thai woman in her 20s who was residing in Belgium and she had been treated prior to receiving maraviroc with isoniazid and cotrimoxazole, and at the time that was not an exclusion criteria, being on isoniazid chemoprophylaxis was not an exclusion criteria for the study. But subsequent to this case that was instituted.

During the weeks leading up to her enrollment into the study her liver enzymes went up from an ALT of 19 to an ALT of 102 and her AST also went up. She started to receive maraviroc once daily and, actually in error at the site, they mistakenly gave her 150 mg once a day instead of 300 mg once a day. She was randomized into the maraviroc QD arm, and she developed a rash and the maraviroc was stopped after five 150 mg doses. However, her INH cotrimoxazole and combivir were continued and she was started on Kaletra and also subsequently to this received 11 gm of parenteral

acetaminophen during the time that her LFTs were rising.

On the day after maraviroc was stopped her transaminases went up dramatically and continued to go up while she was receiving continued INH bactrim, combivir, Kaletra and parenteral paracetamol. Subsequently, obviously, her LFTs worsened substantially and finally resulted in a total bilirubin of 33.4 and a decision was made to transplant her. She actually did well and was ultimately discharged from the hospital to home.

We subsequently actually did some genetic tests and she had the NAT2 alleles 5 and 6 that are associated with slow acetylation phenotype, and also had the CYP 2E1, C1, C1 genotype and both of those collectively increase your risk of INH-induced hepatotoxicity over 7-fold. So, we also had an external hepatologist review the case, and I think the assessment was that this was most likely INH-induced hepatotoxicity.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: There were analyses of low serum concentrations for maraviroc. In light of the BID dosing for efavirenz, were there comparable data for efavirenz and low serum levels? Was that submitted?

DR. MISHRA: No.

DR. HENDRIX: Dr. Havens and then Dr. Hagedorn.

DR. HAVENS: I had a couple of questions of clarification. Back on slide 21, I am still a little bit confused about the tropism test used at virologic failure. So, in this screened ESTA group, the tropism test used at virologic failure was still the old Trofile test. Is that accurate?

DR. MISHRA: That is correct.

DR. HAVENS: So, this 14 percent failure with CXCR4 is a minimum estimate of the CXCR4 type virus that was present at that time. Would that be one way to consider that, I mean, since the ESTA is better? So, this did not use ESTA to identify those.

You made a comment about the 37 in the line below that on slide 21 or 22. Below the level of quantification for the tropism assay, it wasn't clear to me that if the ESTA had been used, a similar way to ask the same question, would ESTA have found those or those were just not testable? Is that right?

DR. MISHRA: Yes, they had less than 50 copies/ml.

DR. HAVENS: So, they would have been untestable by

either assay.

DR. MISHRA: Yes.

DR. HAVENS: So that I understand, on slide 13 it seems that maraviroc works better in clade B compared to clade C when you look by subtype alone because that would, of course, be confounded by more clade C outside the U.S. than in the non-U.S. samples by HIV subtype in that stratified analysis, the last two lines. So, this is people outside the U.S.A.

DR. MISHRA: Yes.

DR. HAVENS: And then by clade B or C.

DR. MISHRA: Yes, that is right.

DR. HAVENS: Were there enough clade C in the U.S. to be ableB-well, no; I guess not, obviously.

DR. MISHRA: The number of subjects in the U.S. was very small so we cannot make any conclusions based on those subjects.

DR. HAVENS: And just one last question, the PK data looked like it was done on the original data set, not on the ESTA data set. Is that accurate?

DR. KRUDYS: It is the ESTA data set.

DR. HAVENS: It is the ESTA data set?

DR. MISHRA: Yes.

DR. HAVENS: Thank you.

DR. NEATON: A follow-up question on this issue while this slide is up, could either the sponsor or the FDA clarify whether in any of these subgroups there is evidence of treatment by subgroup interaction or are we just looking at sampling variability?

DR. ZENG: This is Wen Zeng, staff reviewer from FDA. We did an interaction test and the p value is like 0.07, 0.08. So it is marginal.

DR. NEATON: So, these differences potentially could just be chance.

DR. ZENG: Yes, and also, if you remember, this is a post hoc subgroup analysis.

DR. HENDRIX: Dr. Hagedorn?

DR. HAGEDORN: I had a question about the percentage of patients that were co-infected with hepatitis C in this study. Then I also had a follow-up question on the one patient that had the liver transplant and the 11 gm of acetaminophen. Was that given over a very short period of time or is it known over what period of time that was administered?

DR. MISHRA: I will have Pfizer respond on the duration of acetaminophen use. I don't recall what the duration of use was.

DR. HENDRIX: Pfizer?

DR. HAGEDORN: What about the percentage of patients that had hepatitis C in this study?

DR. MISHRA: Yes, this percentage was very low. It was more in the treatment-experienced population, but still the percentage was low and they are planning a separate study for hepatic impairment in hepatitis B and C co-infected patients with HIV.

DR. MAYER: I can address the duration of parenteral acetaminophen. If you can show slide S-27 again?

[Slide]

That shows the duration. So, the acetaminophen was given over approximately five days. You can see that in the blue on the lower portion of the slide. About 7 percent of patients in each treatment group in 1026 were co-infected with hepatitis C and had detectable HCV RNA.

DR. HENDRIX: Miss Swan?

MS. SWAN: Did everybody get a genotype and a phenotype test at study screening or only after virologic

failure?

DR. MISHRA: We will have sponsor answer that question for us.

DR. MAYER: Yes, patients had a genotype and phenotype for RT, for reverse transcriptase, before and at the time of virological failure.

DR. HENDRIX: Mr. Marco and then Dr. Veltri.

MR. MARCO: I am not sure this question can be answered either by the sponsor or by the agency, but it appears that in the failures in the maraviroc group it is possibly due to background lamivudine resistance that we are seeing come up. Is that possibly the case also with the initial QD arm that was discontinued? Do you have any resistance information on that initial group of QD patients?

DR. MAYER: Thank you for the question. Just to clarify, the question is whether patients in the maraviroc QD arm also failed with lamivudine resistance, or there was evidence of some failures in the QD arm.

MR. MARCO: Yes, but if you have sort of a breakdown. Maybe, I don't know, if both you and the agency want to answer this.

DR. MAYER: I would like to call up Mike Westby to

address the question, please.

DR. WESTBY: Thank you. We don't have the full data set for the QD arm because it was discontinued as it was enrolling. As Dr. Mayer presented, during the ESTA analysis the response went up primarily because screened into the QD arm, we think by chance, were a few more patients with dual or mixed tropic that were not detected by the original assay.

As I presented, all of the patients who have CXCR4-using virus also carried M184V so we didn't see any difference in the type of resistance that we saw in the small data set, but we did see some patients with CXCR4 that was not detected at baseline, and they all had M184V.

DR. HENDRIX: Dr. Veltri?

DR. VELTRI: Yes, I just had a clarification question perhaps, just so I understand the sequence here. It is a question mostly for the FDA. Is it correct that the previous analysis, prespecified analysis, which had a DAP was approved and the secondary analysis, the new high sensitivity analysis was conducted while the trial was still blinded? I think the answer is yes but I am not sure.

DR. PROESTEL: I am sorry, are you asking about the

enhanced sensitivity analysis?

DR. VELTRI: In other words, the original assay which was less sensitive, before the analysis with the higher sensitivity was done, the results from the original assay, those results were still blinded. Is that right? I am trying to figure out the sequence.

DR. HENDRIX: Go ahead.

DR. MAYER: So, the 48-week results from the study with the original Trofile assay had read out but the reanalysis that was done with the enhanced assay was done in a blinded fashion by Monogram with no access to treatment assignment or clinical outcome information. So, the 48-week results had read out from the original assay but the reanalysis was done blinded to the study outcome or treatment assignments.

DR. VELTRI: So, the original analysis results were available. Then my second question from a process perspective, I think I heard this, but the reanalysis with the higher sensitivity that was now specified by the sponsor, was that data analysis plan agreed on by the FDA as well?

DR. PROESTEL: Yes, we discussed that with them.

That is what actually led to the delay in the application. Originally it had been intended to be filed at 48 weeks, and following our conversations with them the decision was made jointly to file the 96-week data.

DR. VELTRI: The reason I am asking is because in follow-up to my original questions on the completers analysis versus last observation--it is the completers and Dr. Neaton's question--is that obviously the numerator and denominator kind of agreed to therefore, and there was some insight from the original output on the less sensitive analysis. But the FDA agreed that the higher sensitivity analysis was to go forward as it was done.

DR. PROESTEL: That is correct.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: Could I just clarify? In this discussion about going forward with the high sensitivity assay, which seems to make a lot of sense, was there a prespecification of which time point was going to be primary?

DR. PROESTEL: As I recall from the conversations, we did not intend changing the primary endpoint, which would still be the 48-week data, but the 96-week data would be

considered supplemental in our analyses.

DR. NEATON: So, from our point of view the 48-week data is still the primary kind of results we should focus on, with the 96-week being supportive.

DR. PROESTEL: Well, you know, advisory the committee can decide what they wish, but the prespecified analysis and the one that remains is the 48-week data as the primary endpoint. I guess you could say that the FDA views the 96-week data as important supplementary data but the primary remains, and always was, the 48-week data.

DR. HENDRIX: To follow-up, Dr. Grant?

DR. GRANT: I was also interested in the statistical analysis plan and how the non-inferiority margin was calculated or how that goal was set. Was that a data-driven calculation of the non-inferiority margin or was it based on clinical judgment that a 10 percent decrement would be clinically significant?

DR. MURRAY: I will answer that one. We have used 10-12 percent for active control trials in treatment-naive patients where we are comparing the activity of the anchor drug in a HAART regimen, so basically the efavirenz position. That is an M2 so that is a clinical judgment.

So, that is why we probably had a little more wiggle room because to show that you are better than placebo--you know, two nucs combivir--you know, the undetectable rate at 48 weeks and 96 weeks would have been negligible.

So, to show that you are better than placebo your non-inferiority margin could be, you know, really huge. It could be 30 percent or more, even taking into account confidence intervals.

So, 10 percent is a clinical judgment. So, if it is a little above 10 percent or a little bit below is not such a big deal really because at the end of the day we are all going to have to figure out, you know, what is close enough to the, quote, gold standard. So, that is why you take another issue, you know, such as safety and resistance. So, you know, 10 percent is an M2 and it is a clinical judgment and, you know, some sponsors in the past have used 12 percent.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: Is FDA able to summarize the universe of PK data to help us understand potential correlates to low drug exposure?

[Slide]

DR. KRUDYS: So, we looked at certain factors like weight and race and we didn't find any big impact for those on exposure. We also looked at BLQ data, and in the 31 patientsB-if I could have slide 32, I think it is or 33B-

[Slide]

Yes, this one. So, we looked at the 31 subjects with low exposure. About 14 of those had a BLQ value. That means that, throughout the course of 48 weeks, there was at least one sample that was a BLQ. For the other subjects, they did not have any samples that were of low exposure BLQ.

DR. ROLAND: And what about data outside of this study?

DR. KRUDYS: We didn't look at data outside the study. Oh, from the two studies for human experience population and covariates there, again, it did not have a big impact on the exposure in those patients. The current dosing is a bit lower if you are taking a PI so you have higher exposure in those patients. But after this study we didn't look at the risk factors.

DR. HENDRIX: I have a follow-up to that question. Data was presented earlier that there was a big food effect presumably observed in that population. I am not sure how

much of that was observed, but you clearly looked for food effects and there weren't any food effects in this cohort. Is that right?

DR. KRUDYS: It was a small one. So there is a 10 percent food effect. The problem with this is the measurement of food or fasting so PK samples were taken over the course of 48 weeks. Some were taken at fasted, some at fed, some not reported so it is hard to say exactly the effect of food in this study itself. But in previous studies you saw, of course, a small change between fed and fasting.

DR. HENDRIX: Then, the C-average that you used here, was that the Pfizer C-average that was calculated?

DR. KRUDYS: Pfizer's.

DR. HENDRIX: And did you look at any other measures, other than fitted values for that analysis?

DR. KRUDYS: We looked at C-min, C-average.

DR. HENDRIX: So, they will be very highly correlated.

DR. KRUDYS: Yes, they were.

DR. HENDRIX: Dr. Strader?

DR. STRADER: It seems to me that the BLQ was the

more sensitive measure. You talk about C-average here but then in data that you didn't present but that is in the document you mention that blacks and others have a 17 percent higher exposure, and women have a 13 or 14 percent higher exposure than men. However, those people have a lower response to treatment. So, it is having a BLQ at any point that is more likely to predict whether or not you are going to respond as opposed to a C-average of 65?

DR. KRUDYS: No, it is not true. So, the C-average of less than 65, it can happen in the presence of BLQ or not. So, in about half of those patients it happened that the sample was a BLQ.

As far as the race factors and the age factors, those who are smallB-and we looked at that in the 31 subjects and they didn't explain the exposure in that population. So, in that population of 31 subjects we can't say it is because of race, age or weight.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Just getting back to the original statistical plan, the memo that we were sent on September th
matter either then. I mean, are we to assume that to be

analyzed as a two-arm study now even though it started as a three-arm study, if it were three arms it was supposed to be at 98.75? But, I mean, if it is a clinical endpoint and we are to use our judgment, it is all in about the same area.

DR. MURRAY: I think we agreed that it could be analyzed as a two-arm study and the 97.5 was fine. Because the QD arm was stopped relatively early it was essentially a two-arm trial.

DR. HAVENS: Perfect. Thank you.

DR. HENDRIX: Dr. Pau?

DR. PAU: I am going back to my original question and I don't know if FDA has the answer or maybe Pfizer. With regards to the initial 1,700 patients or so that were screened, and it sounds like based on my math, that about 50 percent of those individuals were screened out because of either not being able to do the assay or that they had X4 or dual tropic.

Among them, did you do an analysis to see whether there are differences in percentage of individuals that you will have to screen out based on CD4 strata? In other words, did the lower CD4 range patients have a much higher percentage that you would have to screen out in order for

them to be qualified to receive maraviroc?

DR. MURRAY: We didn't do that analysis but I don't know if Pfizer can comment on it. You basically want to find out how useful maraviroc will be depending on what your CD4 count is at baseline, what likelihood are you able to use it?

DR. PAU: Yes, so if I have a patient that has a CD4 count of 150 should I or should I not do a Trofile assay for that particular patient versus someone with a CD4 count of 450?

DR. MAYER: If I can show slide E-36, please?

[Slide]

This actually shows the reasons for screen failure, which were predominantly tropism, viral load and resistance. On the left it shows the patients who screened out because of tropism. You can see that 26.1 percent had a DM result and 32.2 percent had an X4 result. Then, there were also patients who screened out because of viral load criteria because we had inclusion criteria for this study requiring HIV RNA of at least 2,000 copies/ml. So, some patients screened out because they had a viral load of less than 2,000 copies/ml.

Although this wasn't in the treatment guidelines at the time and potentially not standard of care, we actually did screen and exclude out patients with RT mutations. You can see here that 13.5 percent of the screened failures had resistance to efavirenz and were screened out of the study, which could have inflated the response rate in the efavirenz group because we did screen out patients who had efavirenz mutations and other RT mutations.

In terms of the second question, if you could show slide E-136--

[Slide]

This shows the breakdown of response rates in terms of HIV RNA less than 50 copies/ml at week 48 by baseline CD4 count. There were patients, although few, who were enrolled with CD4 counts of less than 100 and in those patients the maraviroc response rates were slightly better than the efavirenz response rates, and in the other strata they were similar.

So, even in patients with low CD4 counts the assay reliably tests and predicts who has R5 virus only because maraviroc-treated patients responded well even in the lowest

CD4 strata.

DR. PAU: I guess that was not really my question. My question is among those individuals who were screened out, those with lower CD4 counts, how many of them have R5, or percentage of those individuals?

In other words, if I have a patient in the clinic today with a CD4 count of 150 what is the percentage that they could have R5 that I would, you know, initiate therapy in that patient or get a Trofile assay in that patient?

DR. MAYER: We have the data. We are just getting it.

DR. PAU: You can get back to us later.

DR. HENDRIX: Dr. Van Dyke?

DR. VAN DYKE: Yes, just getting back to the subjects with low drug exposure, I am still trying to figure out if something is going on. In terms of enteric disease that might have caused low bioavailability, I mean, was there any evidence that they were having GI disease that might hv decreased absorption? No? I see a Ano.@ Okay, thanks.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: Just a question back to virologic

failures. You gave us information about lamivudine resistance amongst the R5s, the X4s and, obviously, we are not going to be able to understand the BLQs, but amongst those, 9 percent were non-phenotypable. Do we have any information about lamivudine resistance amongst that subgroup?

DR. MISHRA: No, we don't.

DR. HENDRIX: Is Pfizer ready to answer that question?

DR. WESTBY: Could we just clarify? For the patients who were non-phenotypable at screening, they were excluded from the studies.

DR. McGOVERN: No, no, amongst those who were the virologic failures or, in other words, amongst the 86 of your patients who were virologic failures you have information about lamivudine resistance amongst those that had R5 at failure, X4. Tou don't have information about BLQ, for obvious reasons. But then amongst the non-phenotypable, do you have information on lamivudine resistance?

DR. WESTBY: I would say for most of those, the non-phenotypable, both tests failed. There were only small

numbers where there was an invalid trait result but a valid resistance result, but we can get that data. The number, though, was quite small where we have data in one or the other.

DR. McGOVERN: So, you did look for lamivudine resistance?

DR. WESTBY: Yes.

DR. MAYER: I am sorry, we don't have the slide but I can just tell you that we actually worked with Richard Harrigan and published epidemiologic data looking at the relationship between CD4 count and having an R5 result. This was published back in 2005, which showed that basically if your CD4 count is below 100 your likelihood of having an R5 result is about 50 percent but it progressively goes up with higher CD4 counts.

But, again, we think that based on the results we have shown in the different CD4 strata that the enhanced assay analysis reliably predicts an R5 result even in patients with low CD4 counts. We have also looked at this in our own screening database, which we presented a couple of years ago at the HIV entry workshop, which shows very similar results, that at the lowest CD4 counts their

likelihood of having an R5 result is less than when your CD4 count is higher.

DR. PAU: So, the 2005 paper, I assume, was using the original assay and not using the ES assay. Correct?

DR. MAYER: Yes, that is correct.

DR. HENDRIX: There was a follow-up question to that previous line of questioning from Dr. Grant.

DR. GRANT: This is a question actually for the sponsor regarding baseline resistance testing. I understand that you did standard clinical genotyping assay and excluded people with RT resistance, and then later went back and did a more sensitive assay for tropism and reanalyzed the data.

Did you have opportunity to go back and redo the RT genotyping using the more sensitive assays that are currently available? I notice that you do cite Jeff Johnson's data which nicely shows that minor efavirenz resistance variants can contribute up to seven percent of efavirenz' failures.

DR. MAYER: No, we did not go back and do that.

DR. GRANT: A follow-on to that, which genotyping assay was used? Even the standard genotyping assays can vary in their sensitivity for minor variants depending on a

number of factors, including chemistry and how the software is set up for base culling.

DR. MAYER: Thank you for that. So, Monogram Biosciences did both phenotypic and genotypic testing at screening and patients were excluded whether they had phenotypic or genotypic evidence of resistance. So, it was the PhenoSense GT assay that was used.

DR. GRANT: And do you have information about the sensitivity of the PhenoSense GT assay for detection of minor RT resistant variants?

DR. MAYER: Sorry, I don't have it to hand. We can get that but we don't have that to hand.

DR. GRANT: Is it anything close to the sensitivity for detecting X4 viruses in the Trofile assay, which looks like it is down around 0.1 percent?

DR. MAYER: I need to get back to you on that.

DR. GRANT: Thanks.

DR. HENDRIX: Mr. Marco and then Dr. Neaton's will be the last question.

MR. MARCO: I guess this question has a little bit to do with Dr. Neaton's question on slide 13 and if there was a difference around the clades. The agency said that,

no, it was maybe more noise than a true difference. But on table 5 of the document from the agency you do note that with respect to race there was a difference noted in blacks in the maraviroc group either at week 48 or at week 96. We also see this in all non-white groups. Non-white groups made up about 143 out of the 167 in whites. Is this noise or is this something?

DR. MURRAY: It should probably be considered exploratory analyses and hypothesis generating. I mean, an interactionB-did you say it was 0.07? That is not a bad p value for an interaction. You might want to comment.

The reason we did this is because we do approve drugs for the U.S. population and we thought it would come up as a question we thought that looking at the U.S. population and the clade that is found in the U.S. population is important subgroup analysis at least to look at. So, that is one of the reasons why we focused on that. Greg?

DR. SOON: Greg Soon, statistical team leader, FDA. You know, for a general interpretation for the p value for interaction the problem is that it is really hard to find an interaction in any trials. So a p value of 0.007 or 0.008

that, you know, it could be a signal because it is so hard to detect.

DR. PROESTEL: Just to follow-on, these analyses were not powered to be significant, so just to reiterate what Greg was saying.

DR. NEATON: I will just comment. I mean, it is true there is lower power for looking for an interaction test. If these were post hoc I think we should view them more for our entertainment than for making anything kind of serious out of them because it is hard. So many subgroup analyses in the past have just been misleading. My question is did the FDA do any analyses related to time to virologic suppression?

DR. MISHRA: No, we did not.

DR. HENDRIX: There being no more questions, the next item would normally be speakers from the public but no one has signed up.

DR. MISHRA: I have a clarifying comment. On the hepatotoxicity and the subject who got liver transplant, I think I mentioned that the patient had high HCV viral load. That is not correct. The patient had hep C antibody present but she had undetectable viral load.

DR. HENDRIX: We are going to skip the public open hearing because no one signed up for that and that brings us to the break for lunch. We will reconvene in this room one hour from now, at 12:30. Please take any personal belongings you may want with you at this time. Again, panel members please remember that there should be no discussion of the meeting during lunch amongst yourselves or with any members of the audience. Thank you.

[Whereupon, at 11:30 a.m. the proceedings were recessed for lunch, to reconvene at 12:30 p.m.]

A F T E R N O O N P R O C E E D I N G

DR. HENDRIX: Good afternoon, everyone. I hope you all had a pleasant lunch and you can still stay awake for the action this afternoon. Before we start with the charge to the committee, I think there was one leftover question and Pfizer wants to answer that.

DR. MAYER: Thanks for that. So, we looked at exogenously administered estrogen-based hormone therapy, and of the women on maraviroc 23.1 percent and on efavirenz 26.5 percent.

DR. HENDRIX: Thank you. Now we will proceed with the FDA charge to the committee from Dr. Birnkrant.

Charge to the Committee

DR. BIRNKRANT: Thank you. I wanted to thank the committee members for the lively, thoughtful discussion this morning, and I wanted to comment that normally we bring a new molecular entity to the committee.

This time we brought a compound that we had brought to you prior but now we are asking you about this new patient population. So, clearly, we had some concerns about the data that we had reviewed, and based on the presentations and the discussion today we have highlighted

that.

Specifically, we wanted to bring to your attention the use of the enhanced assay; the outcome data with regard to reasons for discontinuation, namely virologic failure versus adverse event issues; durability issues with the 96-week data, etc.

In addition, we wanted to share with you our analyses that we conducted looking at exposure response, and we have a question related to TDM in that regard.

We feel that the safety data presented by both FDA and the applicant are reassuring. When we originally presented the application, back in 2007, there were concerns based on the mechanism, etc. There were a few cases of hepatotoxicity, in addition, there were cases within the class. So, there were concerns back then and with this larger database it is somewhat reassuring with regard to the adverse event profile of the product.

It is important to have options for patients, but it is also important not to lose sight of risk/benefit and I think we need to consider that in our deliberations this afternoon, or in your deliberations this afternoon, because it is important in the end to be able to describe the

risk/benefit of a product so that providers, as well as patients, can make the most informed decisions that they can with regard to their treatment.

So, with that, we have five questions for the committee outlining various aspects that were presented to you this morning and we have basically one vote question. But we will start off with number one, which highlights the use of the enhanced sensitivity Trofile assay. So, please discuss the use of the reanalysis of the efficacy data using this enhanced assay to support efficacy for the treatment-naive population for maraviroc.

Questions for Discussion

DR. HENDRIX: Thank you. So, we will now begin the panel discussion portion of the meeting and respond to this question. We will do them one at a time as we work through them.

Again, although this portion is open to the public observers, the public attendees may not participate except at the specific request of the panel. I will go ahead and open it then to the panel for points of discussion or you can ask questions at this point of anyone that you can get through in the room or the panel, and you can make comments

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as well. Dr. Havens?

DR. HAVENS: As shy as I am, I figured somebody has to break the ice. So, this morning it wasn't clear from the response to a prior question is the enhanced sensitivity Trofile assay FDA-approved for use in the United States?

DR. PROESTEL: That is a difficult question to answer. I think at this point it is unclear whether FDA will regulate this test. It is available and--

DR. HAVENS: I understand. I didn't ask about available. I understand. The company actually made it quite clear it is the only available test over and over again. So, I understand it is the only available test right now but there are other tests that people are looking at. So, the question I would have for the FDA is are you suggesting then that maraviroc would be FDA-approved for use only in people who had a Trofile assay done by Monogram Biosciences which has the performance characteristics that we have been exposed to here?

DR. MURRAY: Well, we will have to probably struggle with that in the labeling. I don't know if we want to burden the committee with that because it really is a regulatory issue related to putting the sponsor of a test or

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a certain test that is unapproved in an approved label that might cause some regulatory problems and at this point I think it is still kind of a question whether these tests, which are basically done in-house and not marketed as test kits. So, it is kind of unclear where they fall in the regulations.

So, we are going to have to figure out how to put that in the label, you know, what test must be used. I would think that we would probably just describe the test that was used in the clinical study section and say that an enhanced test was used. Again, it comes down to labeling and it is going to be a little bit tricky and that is kind of the best answer I can give you. I know it is not satisfactory to anybody because it is not satisfactory to me.

DR. HENDRIX: To follow-up on the same thing, we were in the same situation when this first came two years ago, I think, when this came before the board, this license issue of yes or no, and how did FDA deal with it then? I am not saying that you would necessarily do that but what is the history on the similar situation with this disconnect between a licensed product and an unlicensed test but a

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clear connect in terms of how the drug was studied?

DR. MURRAY: Well, it was a little easier I think back then because there was just one test and one version. And, there have been multiple discussions. I mean, I think all that I can tell you right now is that it is an unresolved issue and I think it is going to have to, unfortunately, be up to maybe guidelines perhaps, maybe treatment guidelines, etc. to point out, you know, the most appropriate test to be using. It is kind of falling in the regulatory vacuum or dead zone right now and, you know, it is something that the agency is going to have to grapple with but I don't think there is going to be a quick answer, certainly not for your deliberations today.

DR. BIRNKRANT: But, clearly, the indication reads for CCR5 tropic virus. So, that I believe is clearly stated in the label. And, given what we have learned with this new assay compared to the old assay and the differences in outcomes, etc., we would clearly have to describe the performance characteristics of the assay that supported the new data, if that were to be included in labeling, because there is such a difference between the original assay and the subsequent assay. So, I think it would be important to

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include characteristics if we go in that direction.

DR. HAVENS: But Dr. Grant made a point earlier about the parallel construction for finding efavirenz resistance, and if you had done a reanalysis of susceptibility data based on efavirenz resistance, you know, the 103 failures in the efavirenz arm would have been likewise much smaller because you might have excludedB-well, it is the same kind of issue. So, it might have made maraviroc look less good in that context compared to a comparator drug that had equally intense, extra intense screening prior to its use.

DR. BIRNKRANT: Your point is well taken and we will have to deliberate back at the agency.

DR. HAVENS: Thank you very much.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: Given the current context of available tropism assays, it seems like it was entirely appropriate to do this analysis using the more sensitive assay on the screening samples.

One of the things that I had not recognized in reading the background materials, but it seems to have been uncovered here pretty obviously, is what appears to be a

significant weakness in not having reanalyzed the baseline samples and the failure samples. So, I think that is something that we need to really think about. What could the potential impact have been on the outcome had those baseline and failure samples also been reanalyzed with the more sensitive assay.

DR. HENDRIX: Dr. Pau?

DR. PAU: I actually have the same comment that Dr. Roland had.

DR. GRANT: Can I comment?

DR. HENDRIX: Go ahead.

DR. GRANT: I mean, the key issue is whether the new assay would have scored as R5 any people who were found to have X4 viruses initially and who were excluded from the study on that basis. I think that they should have done those tests. It wouldn't have been very cumbersome to just reanalyze to make sure that the more sensitive assay didn't lose anything or didn't miss any excluded cases.

But, you know, the company is stating that they don't think that any of the people who originally were excluded from the study because of X4 would have been able to enter the study using the new test. So, I think the

analyzed data set does represent the people--if that is true, and we would like to see data if it is obtainable. But if that is true, then I don't think there would be a difference between the analyzed group and the group that would have entered the study.

DR. ROLAND: But it would be different if the ones that were analyzed as R5 at screening turned out to be X4 at the baseline.

DR. HENDRIX: Oh. But what would the effect of that be? I mean, I think that would reduce the differences that exist because the virologic endpoints are what they are. I mean, the endpoints aren't different.

DR. ROLAND: Well, it depends on whether--

DR. HENDRIX: You would have missed some that you would have liked to have screened out but, as it is, it seems they move in a different direction. I don't know if it moves in that direction it would change the way you would interpret the results.

DR. ROLAND: I think looking at the baseline samples and looking at failure samples are a different question. So, if we saw a higher proportion of people switching tropism between screening and baseline that would

raise a whole other set of clinical concerns about the utility of this test and how quickly you have to get people started on drug. If we saw more people failing with more dual and mixed tropic virus, that would also raise a whole other set of clinical concerns about the potential implications of the drug.

So, I am not implying that it is a fatal flaw to not have that information, but--

DR. HENDRIX: It would be useful additional information in terms of management.

DR. ROLAND: Yes, and I just want to make sure that we are carefully thinking through are there any potential implications that are really critical as opposed to just the information would be nice to have.

DR. GRANT: You know, I think they did want to run the study to represent a clinically feasible practice, and in practice it is not clear how you would order a baseline test and make a decision to start maraviroc on that same day even though you don't have the results of the baseline test.

So, you know, presumably you might argue, well, given that there is known fluctuation in X4 virus populations, maybe you need more than one screening test in

order to assure yourself that this person has a persistent R5 virus population. But then you are talking about adding two expensive and cumbersome tests prior to starting maraviroc.

I guess what I wanted to clarify is I don't see how clinically it is feasible to really get a baseline R5 result that you can use because you are having to start the drug on that same day. You are never going to get that result on the same day. So, in practice what you have is an ability to screen patients and then make the decision based on a prior screening test.

But, Michelle, your point is well taken. I mean, I think that clinicians would need guidance as to how recent the screening test has to be and that should be described very clearly, how many weeks you have between your screening test and the time of starting. It would be reasonable to start I think with the amount of time that they had in this trial. I guess the question for the company would be how long was the time. What was the range in average time between screening and starting maraviroc?

DR. HENDRIX: Dr. Pau?

DR. PAU: I know that I go back to the same

question over and over again. I think it is important for the public to know or the prescribers out there to know, by the time--if this drug becomes approved for initial therapy, during the screening process what percentage of individuals who had a low CD4 count or a medium CD4 count got screened out because of not having R5 only using viruses. That will help to guide the physician as to when and if a patient would be someone that you would do a Trofile assay for, which costs quite a bit, in making that decision process.

So, I think that I was quite surprised in most of the studies that I have seen. They will have the whole algorithm of number of people screened, the number of people screened out and the reasons behind them. Those data were not available for us to really digest, which were available at the time when maraviroc was approved for treatment-experienced patients but I didn't see it for the treatment-naive patients.

DR. HENDRIX: Pfizer, or sponsor, there was an earlier question that I think you wanted to respond to and I missed you. Did you want to respond to the prior one, and you may well want to respond to this as well.

DR. MAYER: Yes, it was just that, again, the

reanalysis was conducted to take the sample that would normally be done, as Dr. Grant was saying, to determine whether the patient was appropriate for maraviroc.

The average turnaround time for the Trofile assay is about two to three weeks. So, as Dr. Grant was saying, you wouldn't be able to really act on a baseline sample so we chose the sample time that would represent when someone would do the Trofile assay.

In terms of the CD4 count, we can easily get those data in the screen failures. About 17 percent of the screen failures were related to DM or X4 virus and, as I mentioned, in the treatment-naive population your risk of having that is higher with lower CD4 counts. But we can definitely provide that data in the future.

DR. HENDRIX: Dr. Van Dyke and then Dr. Neaton.

DR. VAN DYKE: Yes, I may just be restating what I said before. It seems to me the question for me is that the patients that were finally analyzed in the second data set are really subjects that have been screened twice. They passed the standard Trofile assay and then those that passed were screened again with the enhanced assay.

We would like to know what would have happened if

everybody had been screened initially using the new assay. And, I think what is left out is those that failed the first assay and it would be useful to look at that data. I mean, we can presume that it would have worked as well but it would be nice to see that data.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: I was just thinking about Alice's question which I think is a good one in terms of understanding. Can you tell us the CD4 cell count at baseline for the people that you omitted based upon the sensitive analysis, how they fell out by CD4 cell count?

I mean, while you were talking about it, the word Ageneral@ is very tangential to the question. It seems like you are dealing with a situation here where there is a clear relationship with CD4 cell count and you are going to have many more screening failures at lower versus higher counts. Unfortunately, the study was primarily focused on lower counts.

So, when I think about where the drug might be used if you want to reduce screening failures, we don't really have a very good risk/benefit analysis. There were very few people that came into this study with CD4 cell

counts that were high.

DR. HENDRIX: Can you point us to where that is because I didn't have that impression?

DR. NEATON: Well, the baseline CD4 cell count--I think they had a slide. I think there are only about 60 people over 350. The median CD4 cell count at entry was 240 I believe. But maybe you could just respond to my question. That might shed some light on kind of whether there is differential loss by baseline CD4.

DR. MAYER: Just to say again, and I think this was presented, we looked at the demographic and baseline characteristics of those patients in the original analysis and also those patients who were confirmed to be R5 by the enhanced assay. And, the demographic characteristics were similar in the two treatment groups, with the 106 patients excluded who were found to have X4 by the enhanced assay. But we have also the screening characteristics for those patients who were screened out versus those patients who were confirmed to be R5 by ESTA.

If you could show slide E-41, please?

[Slide]

So, this shows the demographic and baseline

characteristics for patients who were found to have CXCR4-using virus by the enhanced assay, and then R5 tropism by the enhanced assay, on the right. If you look at CD4 count, for CXCR4-using virus, for those patients who were screened out had--255 was the median on maraviroc and 230 was the median on efavirenz, and 236 versus 254 for those patients who were confirmed to be R5 by the enhanced assay.

DR. NEATON: If I calculate this correctly, the median CD4 cell counts, at least for the new people that were excluded, are similar to those that were originally--

DR. MAYER: Yes, that is correct.

DR. HENDRIX: Are there other points to be raised in discussion of the first question? Yes, Dr. Van Dyke?

DR. VAN DYKE: Just a follow-up on that. I wonder about the CD4 counts of those that were excluded in the first Trofile assay. Were those CD4 counts comparable?

DR. MAYER: We don't have that. I mean, with the first Trofile assay there were many reasons for people actually being screen failures, among which was CXCR4-using virus but there were also other reasons for screen failure, not meeting other inclusion or exclusion criteria. So, those wouldn't be expected to necessarily be influenced by

CD4 counts. But, again, we could provide those data to you.

DR. HENDRIX: Dr. Roland

DR. ROLAND: I was just wondering if FDA has specific concerns and why this question was raised for us to discuss. Because, to me, it seemed relatively straightforward, what they did, and I didn't have any obvious concerns. I don't feel like we have raised any huge concerns. So, I am wondering why we were asked this specific question.

DR. MURRAY: Well, before we got to the vote question we just wanted to make sure we elicited all the potential conversation about efficacy and safety, and we thought doing a reanalysis for, you know, a primary endpoint is a little bit unusual in using a new assay so we just wanted to get it out there, not that we had strong concerns about it ourselves.

DR. HENDRIX: We are not voting on this question but let me just askB-there are a couple of points that I will summarize in a moment, but are there any strong objections to using this, to using the reanalysis with the newer technology to make the judgments about non-inferiority in these trials?

[No response]

Dr. Neaton?

DR. NEATON: Just to say it in a different way, the consequence in my mind is that you now have many fewer patients, 611, I believe, or whatever it was, 614, with lower CD4 cell counts on average that have been studied with this drug kind of to look at the risk/benefit. That is the big consequence of this exclusion in my mind. It is a smaller kind of trial in order to kind of weigh the risk and benefits.

DR. HENDRIX: Dr. Grant?

DR. GRANT: I have concerns. You know, essentially what is being done here is that they are taking a lot of data and a lot of experience which gives them an understanding of why maraviroc fails and then, in a post hoc way, they are tightening up their enrollment criteria to try to minimize those failures. And, it was only done for one side of this trial.

The clinicians in the room can speak more clearly than I, but we also have a lot of information about why efavirenz fails. I mean, it typically fails when there are minor variants that are resistant to efavirenz. We have

already talked about that. But there are certain patient populations which are well-known to have tolerance issues with efavirenz and I believe they are black and African-American populations and, you know, this trial is heavily populated with the patients that, in fact, are known to have difficulties with efavirenz.

So, you know, I think that in a post hoc way they tightened up the enrollment criteria to give maraviroc every chance it could have. They didn't really do the same due diligence for efavirenz. So, I think that is the concern.

DR. HENDRIX: But what about the resistance testing? At the beginning they excluded the efavirenz resistant--

DR. GRANT: But there are better resistance tests for efavirenz.

DR. HENDRIX: So, there is an evolving technology as well.

DR. GRANT: But I am capable of arguing both sides of this. On the other hand, what for me is pivotal is that this extended sensitivity Trofile assay is the standard assay available at this time and the genotypic assay that they used to screen for efavirenz treatment is also the

standard assay. So, just because they could have pushed the envelope more on efavirenz doesn't mean that that is feasible for a clinician now to order any of the ultra sensitive tests. It is not for efavirenz resistance.

So, I think that they were fairly comparing the standard of care but the standard of care got pushed more in the case of maraviroc. I think in this case there is a nice collaboration between diagnostics and therapeutics which improved the diagnostics substantially, and I think that that is why maraviroc is looking better in this case.

But it is a real benefit to the extent that improvements in the diagnostics were real. I think the chance of using maraviroc in a really successful way also improved. But that gets us backB-we are still sort of dancing around, which is that a lot depends on the performance characteristics of this diagnostic assay and it is not being reviewed at this time by this committee.

I just had a simple question, and I imagine this data exists, but was the sensitivity of this assay improved at the expense of specificity? I mean, that is quite simply what we are all sort of dancing around. Did they just test the cutoff so that they can improve their diagnostic yield

but at the expense of people who would otherwise qualify for maraviroc?

I think that is a simple question. I actually believe the data exists and I would just like somebody to say to us the answer to that question. If there is expertise in the audience who can address this, they should feel free to give us that information.

DR. HENDRIX: Sponsor, go ahead.

DR. MAYER: So, to address the sensitivity and specificity I can call up Mike Westby. I think there is also expertise in the audience, if that is required, but I will call up Mike Westby.

DR. WESTBY: Thank you. I will try and address this and if that doesn't work then maybe you can rephrase it for me.

I think what you are asking is did the enhanced sensitivity lead to more patients being excluded who would have benefitted--in other words, people excluded who would have benefitted from maraviroc.

So, if I could bring up slide V-16, please?

[Slide]

I hope this will address it. So, on the left is

shown benefit that was given to the efficacy by the reanalysis that was presented by Dr. Heera. This is looking at the outcome at 48 weeks. We can see that with the ESTA population we did improve the outcome to 68.5 percent.

Shown on the right is the outcome that we got since we had the outcome data for those that were screened as CCR5. So, the bar on the right-hand side matches the bar on the left at 68.5 percent, and those that were excluded, 44.9 percentof those excluded by the ESTA did, in fact, respond.

So, in this population we believe the ESTA test did improve the efficacy but you are right in saying that not everyone excluded went on to fail.

DR. HENDRIX: Just so this is on the record, I asked Dr. Grant if there was someone he wanted to pick on in the audience that could answer the question specifically. I mean, it is a very specific question that this data gets at indirectly but there may be something more specific.

DR. GRANT: So, does the new assay fail to detect a portion of people who would be detected as X4 using the old assay? That is the question. Eoin, could you respond to that?

DR. COAKLEY: Eoin Coakley, from Monogram Biosciences. So, the specificity of the assay remains unchanged. The only attribute that changes is the sensitivity to detect minor variants. And, we have demonstrated that in mixtures, and in a recent publication with Hanneke Schuitemaker with the MT-2 assay, we have demonstrated we have demonstrated better correlation with the enhanced assay and the MT-2 correlates for positive SI assay in cell-based culture.

So, sensitivity improves; specificity remains unchanged. So, we don't see samples go from DM in the old assay to R5 in the new assay. That is not a feature that we expect to see going forward.

DR. GRANT: Thank you. That is exactly what I wanted.

DR. HENDRIX: Miss Swan?

MS. SWAN: Pass.

DR. HENDRIX: I apologize, I was already moving to my next task. Dr. McGovern?

DR. McGOVERN: Just to comment that I also agree that the ESTA reanalysis is reasonable, but I think it is right for the FDA to pose the question as to whether we

think that this analysis supports the efficacy because when we omit 14 percent of the maraviroc arm that had X4 virus at the beginning with the ESTA assay and then we omit 16 percent from the efavirenz arm, as Pfizer has pointed out, that eliminates a lot of people who eventually had failure in the maraviroc arm, but we are also then eliminating from the analysis a lot of people who attained virologic success on the efavirenz arm.

DR. HENDRIX: Dr. Pau?

DR. PAU: I think I am looking more at the bigger picture as well. We are using the enhanced assay to look at the data that are presented to us today. I am thinking down the road. Would that become the FDA's gold standard for evaluating future CCR5 antagonists, given the performance that is being seen here?

And, if there is less expensive other type of phenotypic assay or genotypic assay available in the future, what would it take for those assays to be able to be used for either licensing for the FDA future CCR5 antagonists or that the clinicians can use on the outside to assure that they are actually truly having CCR5 tropic virus and, more down the road, how is that going to impact future drug

approval or future analysis?

DR. BIRNKRANT: Whenever we review outcome data where there is a test tied to it, we obviously have to review the methodology related to that particular test. If it is a relatively new test with not a lot of experience with that test, we would clearly consult our colleagues in the Center where these are reviewed to get their expertise and input in helping us reach a decision whether it is at an early stage, commenting on a protocol, or a later stage when we analyze the data.

For something that is more widely in use we tend to do that type of analysis with regard to the methods in our division, and if there are questions we will obtain consultation with other experts within the agency.

I don't know if that at all got at a portion of your question. Again, as Jeff mentioned, the review and regulation of these assays is not within our division. At this point in time we can't mandate that a company bring their data in-house so that we can review it to be able to make a regulatory determination. So, that is still under discussion.

DR. HENDRIX: Thank you. Jeff, go ahead.

DR. MURRAY: Yes, that could be done voluntarily, submitting for review, but, as Deb says, it is not at this point a requirement.

I guess if a new assay was coming in I think our advice has been that we would want what I guess we consider the standard right now, which would be the enhanced sensitivity Trofile assay, and the new assay, both done and they would have to show kind of the performance characteristics and, you know, the outcome using both assays compared to each other. So, they would have to, you know, compare themselves to what we consider the standard.

DR. HENDRIX: Thank you. Dr. Havens, last comment and then I will summarize.

DR. HAVENS: But then, as we look forward, which we are doing, there were some genotype changes in maraviroc failures. So, finally, you are going to have to expect a much longer Monogram Biosciences phenotype GT printout with maraviroc changes at the bottom in addition to the Trofile because both of those things will need to be taken into account looking at next generation inhibitors which may be resistant for reasons even if they are R5 virus.

DR. HENDRIX: Dr. Strader?

DR. STRADER: I think it sounds like the ESTA test is probably best used to predict the probability that somebody with CCR5 or CXCR4 virus might respond to maraviroc as opposed to excluding people. If we look at this we see that is what they just showed, 45 percent of people who were CXCR4 still responded to this.

So, somehow the idea that we use this test to exclude people doesn't sound quite as reasonable as using it to predict what your likelihood of response is depending on what the assay shows. So, I think we are probably looking at this as though we are going to exclude people from being treated with a drug rather than saying they may all be treated. But these people with this result have an X likelihood of responding, and these people with Y result have a different likelihood of response.

DR. HENDRIX: So, let me summarize the discussion on the first question from FDA. I think there was a general consensus that it was a reasonable reanalysis. There were a couple of caveats in specific categories.

There remains the unresolved issue of the unlicensed test and how that is going to be handled in the label, and the importance of the performance

characteristics.

There is room for more useful clinical information in terms of baseline endpoint sampling in terms of having the data at later points to guide issues about how recent a test ought to be and how frequently it ought to be used but, again, these focus on the test itself.

There was discussion about the CD4 counts and the representative nature within the study, although the studies also happened in a climate of the pendulum screening in the other direction in terms of perhaps earlier treatment based on CD4 counts.

Then, sort of the evolving technology of the envelope that is moving continually in terms of the standard of care, in terms of technology, to make selections of who might and might not benefit from maraviroc, and how that balances against efavirenz, which is a consideration in interpreting the comparison of the two.

So, we will go ahead then. I guess, FDA if you want to make comments on the second question or shall I just go ahead and read it?

DR. BIRNKRANT: The second question gets at subject disposition and the concern that we found with regard to

reasons for discontinuation or failure. So, in the maraviroc arm more appeared to fail for reasons related to lack of efficacy, whereas in the efavirenz arm it appeared as though there were more discontinuations due to adverse events. So, we would like the committee to compare those two outcomes and the impact that they may have in regimen selection for patients.

DR. HENDRIX: Let me just read the question again because there are two parts to this in terms of both resistance and the adverse events in contrasting the differences there.

Discuss the relative increase in the virologic resistance that was observed with maraviroc and compare this to the relative increase in adverse events that occurred with efavirenz.

DR. NEATON: I don't mind starting this. As I mentioned earlier, it seems to me when you have an endpoint like this where you can think of it as being a composite, if you turn it around there are a lot of reasons for being a non-responder, for being in the denominator but not in the numerator of their tables.

When they are so varied and when one of them

relates to the specific efficacy outcome that you are looking at, virologic response, and they are going in different directions you have a problem with the endpoint. That is a general problem with using a composite like this.

So, I think in that situation you need to kind of break it down, and the breakdown that I think we have is the number of people that were actually tested for viral load, for example, at 48 weeks. There is a subset of those that were, quote, non-responders, a small number that had viral loads greater than 400, and a larger number of people that failed virologically beforehand. If you consider those numbers, there is almost a 10 percent difference in the failure rate virologically at 48 weeks, not the upper bound, just the point estimate for the failure rate.

So, if you look at figure 2 on page 26 of the sponsor's report, this is the only place where I found actually some data that tracked the viral loads over follow-up, and the reason for asking the question earlier being that all the data suggest to me that there is a more rapid rate of virologic failure, kind of, in the maraviroc arm than the efavirenz arm. You could of kind think of a slower rate of getting the viral load suppressed, which this figure

displays where you see kind of early on in the follow-up period that all the points for efavirenz are higher than maraviroc.

So, just in terms of understanding the virologic efficacy, I don't think the kind of outcome that we saw in the charts that compared the percent less than 400 and the percent less than 50 are telling you the whole story. I actually think it is quite misleading what the story is telling you because of the way it is computed. If you look at the reasons for discontinuation, it appears there is a poorer virologic response with maraviroc than efavirenz by quite a bit.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: So, where would you find the denominator for that so you could really measure it?

DR. NEATON: That is the problem, that in terms of doing the analyses we don't have before us where they have done some type of a time-to-event analysis. And, you are right, that is a problem with discontinuations too because people are leaving the denominator there and we are just seeing counts and percents.

But the raw counts that I computed based on the

figures that the FDA showed were 52 versus 21 failures, failures being defined as a person who discontinued because of virologic failure or who had a measured viral load greater than 400 at 48 weeks. So, in terms of the raw counts it is more than twice as large.

To get the rate, we don't have the number. Perhaps the sponsor could elucidate this, but when I asked the question earlier it didn't seem like the analysis had been done.

DR. HENDRIX: Follow-up on the same question, Dr. Grant?

DR. GRANT: Jim, just to clarify, are you calling for a per-protocol analysis basically? You want the data to be analyzed according to time points where people were actually receiving their randomized regimen?

DR. NEATON: No. No, actually that is what has been done. I mean, what has been done right now, or another way you can think about it is that they are imputing failure for all of the non-responders. Some of the reasons for non-response were lost to follow-up; some were pregnancy; some were AE discontinuation. They are calling them all non-responders per this definition.

The problem with that comes when you have so many, quote, non-responders, and there are a lot of them even at 48 weeks, and they differ for a reason for one treatment or the other. One is virologic, you know, failure and the other is kind of AEs. It is pretty hard to interpret that gemish. So, you have to break it apart if you want to understand virology versus safety.

The only measure of virology that I can find is the people that failed virologically in the first year or had a viral load greater than 400, say, or greater than 50, if you want to use that, at 48 weeks, and that gives you a very different picture in my mind.

DR. HENDRIX: So, if you follow that then you end up with let's say there are simply two categories of response. You have a virologic response, as with this question, a virologic response and adverse event response, yes or no, that go in opposite directions. The composite includes both of those. Do you want to parse it out for each one and make individual decisions?

I mean, in the end the decision is a composite decision to use the drug or not to use the drug based on a variety of factors that this seems to capture. I guess I am

trying to understand. I can see value in parsing it to understand why there are risks and benefits for one product or another but in terms of interpreting, taking all-comers the way the study was designed, is this composite outcome a reasonable judgment, a reasonably useful definition of a response, not specifically virologic, not specifically adverse event? Is that reasonable?

DR. NEATON: That is an arguable question. So, if you ask me personally, I would say no, it doesn't make any sense because you want to be able to understand the efficacy separately from the safety of a treatment. This also has factored into it losses to follow-up, which are pretty high in this trial. Over the first 48 weeks, seven percent versus five percent in the two treatment groups. So, that is all being factored here.

So, I would say you would want to do a better trial and be able to sort out the relative components of that composite. If they went in opposite directions you would have to make a judgment. Do you weight the virology equally with the discontinuation for safety?

DR. HENDRIX: To follow-up on that point, I think this is critical. The FDA asked this question and it gives

the clear impression that it is their interpretation that there is a clear difference in virologic response when that is parsed out, and there is a clear difference in the adverse event profile when that is parsed out separately. Is that your interpretation in those two? I am not sure exactly which page we need to look at to go back to this.

DR. MURRAY: That was our interpretation. That is what we meant by relative increase.

DR. HENDRIX: Okay.

DR. NEATON: I think it is important to point out that when you look at the primary outcome that the sponsor specified, and it is in the data analysis plan, that actually, depending kind of upon whether you look at 50 or 400, is within the bounds of non-inferiority. But that is a function of how that is being computed and what is in the denominator there.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Well, your argument is if they did the analysis in the way that you are looking at it, separate efficacy analysis versus withdrawal for side effects analysis, the efficacy analysis might show what they are suggesting, which is that maraviroc might not meet the non-

inferiority criteria in that kind of an analysis for primary virologic efficacy.

DR. HENDRIX: But that wasn't the primary outcome measure.

DR. NEATON: It wasn't but I think that is the reason I introduced this by saying that if you are going to gamble, put it that way, then use a composite outcome that includes many components, and these components mean different things, and all those components don't go in the same direction you have a problem in interpretation. And, that is what we have here.

DR. HENDRIX: Mr. Marco, on this point?

MR. MARCO: Yes, it is. I guess I want to ask the agency with the increase in adverse events, and I know they already gave the presentation, but is the increase a whopping increase difference? I mean is it one or two specific things? Of course, the dizziness, but others and a little bit of the hepatic, there is a little difference but, I mean, if somebody could clarify that a little?

DR. MURRAY: Well, I think in the table that Dr. Mishra showed it was mostly the neuropsych events, the dizziness, but there was some rash but mostly rash and

neuropsych. You know, not horrible adverse events, but adverse events that made people discontinue efavirenz.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: So, a slightly different way of looking at this, I think there is some irony that the adverse events experienced with efavirenz are actually protective in terms of the development of virologic failure and RT resistance. You know, these are not life-threatening adverse events. These are symptomatic adverse events leading people to discontinue therapy before they have a chance to develop resistance.

So, when I look at the long-term consequences and safety questions I am much more concerned about higher rates of virologic failure and RT resistance seen in the maraviroc group than I am about the specific adverse events that we are seeing in the efavirenz group which I think are actually protective.

DR. HENDRIX: So to follow-up, your concern would be perhaps more if there actually was a negative consequence to antiretroviral choices following that resistance. But it turns out that is actually not true in this case.

DR. ROLAND: Well, I disagree with that. What we

were presented with was second-line therapy so, of course, people are going to respond just find to their second regimen because we have options for a second regimen. But what about their third regimen or their fourth regimen? And, we have to be thinking strategically and not just about the next step but all the next steps.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: When you look at just absolute numbers of people who developed virologic failure, 86 on maraviroc and 60 on efavirenz, that is a very significant difference, it appears. Then, when you look at the development of lamivudine resistance and then in the subgroup who developed, you know, triple drug resistance, and then there is this subgroup of people in whom the phenotype couldn't be determined and we don't know the lamivudine resistance profile of those patients, altogether it just gives a lot of concern about how much resistance is developing in a subgroup of these patients.

I agree with the comments about, you know, what that impact could have on future therapies, particularly on a drug like lamivudine that is so well tolerated.

Then, in terms of the second part of this

question, which is the increase in adverse events, you know, most of that increase in adverse events is related to dizziness, etc., from efavirenz which is transient, some with rash. Yes, we might have to discontinue but the long-term consequences of that kind of thing are not as important to me as not having the options of using lamivudine in the future.

When you look at the rates of discontinuation for the entire trial, they are actually rather large when you compare to, let's say, another trial published by Gallant using efavirenz in both arms in background of combivir versus background of tenofovir/FTC. If you look at the arm that is comparable to this trial, efavirenz and combivir, those discontinuation rates are much lower than in this particular trial.

So, you know, in general I just have concerns about those relative increased adverse events that were documented in this trial and, again, the resistance issues which are permanent.

DR. HENDRIX: Mr. Marco?

MR. MARCO: I think Dr. McGovern summed it up beautifully but, I mean, now that we are talking about

resistance versus transient side effects, just dizziness, and this huge rate that we have seen here now, I am on efavirenz and, yes, the first month was at times sort of horrific, a lot of nightmares of missing the Delta shuttle, things like that, but, you know, it is all about travel.

But it is transient, but luckily I have a physician who was able to work with me, let me know when it should be taken, let me know what to expect, and even would say, you know, stick with this; stick with this.

Because this was done in so many different places and so many different settings, in South Africa, that I am not certain that we can generalize the counseling about these toxicities and Astick with it@ message was the same. Resistance is the same, you know. You know, it didn't work as well. That is basically my thought.

DR. HENDRIX: Miss Swan?

MS. SWAN: A few weeks before this hearing I sent an email out to hundreds and hundreds of my peers in Europe and the United States asking them if they had any concerns that they wanted me to raise. And, although people were overwhelmingly happy about the tolerability, losing future therapeutic options, particularly in light of a diminishing

new drug pipeline for HIV, was a significant concern among community members as well.

DR. HENDRIX: Dr. Grant, you had a follow-up to Mr. Marcus' comment?

DR. GRANT: Well, in terms of representativeness, I actually feel like I would like to congratulate Pfizer for including African sites in their study. To my knowledge, it is the first time that we have seen in this committee pivotal trials done in Africa where the majority of people who have HIV are living. So, I think, you know, rather than assume that the care that can be enjoyed here, in the Washington D.C. area, is going to exist in Africa it is better to do what they have done, which is to actually study their drug in Africa.

So, I wanted to mention that there is still more work to be done in terms of representativeness but I did want to mention that for the first time we have seen a pivotal trial done in Africa. What did it give us? It gave us the largest proportion of women in a pivotal trial I have ever seen. I may be speaking out of turn. My experience is limited. It has also given us the largest number of black people in the trial, and it is the only trial that has

presented us with African data.

So, I think that things are moving in the right direction. My colleague, Victoria, presented earlier that there is still an enormous amount of progress still to be made. But it bears directly on your comment about representativeness because I think that we do enjoy the kind of clinical support that could treat through CNS side effects of efavirenz in the United States. But I am not at all convinced that that level of clinical support and sophistication is feasible in resource poor areas that need these drugs just as much.

I also wanted to comment on the resistance. Can I do that? I don't want to blather on here--

DR. HENDRIX: I will let you know when you are blathering.

DR. GRANT: Okay. But not all resistance is created equal. I think, you know, 184V is a mutation which affects lamivudine and emtricitabine. It actually hypersensitizes viruses to d4T and AZT and, to my knowledge, most of the guidelines argue in most cases for continuing lamivudine in the face of 184V because the selection for the mutation is appropriate.

So, I think that the excess in resistance that we see is really only 184V in this setting and, as resistance goes, that particular mutation has proven to be manageable. That would be my claim. Obviously, I would love to hear from the clinicians on that.

But there were other resistance mutations associated with efavirenz failure. I mean, efavirenz resistance was quite common and I think that should be taken seriously too because that closes treatment options.

DR. HENDRIX: Thank you. Dr. Cargill?

DR. CARGILL: I was going to go back and revisit something that Jim raised earlier, which is that I think you are still looking at a composite. When I try to step back and think clinically if I were going to try and make this decision versus, you know, one group where you have individuals that have been lost to follow-up or haven't been taking their medications and putting that altogether with individuals who have had efavirenz-induced side effects, yes, I agree with you, you can get through them. But we also have a population that is a little bit predisposed to this and who have been well represented in this trial. We know that efavirenz challenges occur more often in black

populations.

So, I think we are still back to struggling with how do we go back and forth between these. I think I would have to agree with you, Jim, that having a better sense of what some of this means in terms of people who are lost versus people who didn't take pills or those people who really didn't do well would be helpful.

DR. HENDRIX: Dr. Strader?

DR. STRADER: I also had a question about resistance. It is my understanding that lamivudine-based regimens are no longer considered a first-line drug. We see that lots of patients we CCR5 also have lamivudine resistance, but it seems to me some of the data they presented here suggesting that emtricitabine and something else, I can't remember what it was, is now considered first-line so that that would change the resistance data somewhat. Is that correct or have I misread that information?

DR. MURRAY: Well, I think the emtricitabine and lamivudine share a common 184 mutation. So, I think it would be the same.

DR. STRADER: Because I was under the impression that you would use a different group or two in an NNRTI as

opposed to the ones that were used initially in the study because when the study first started lamivudine and the other drug were considered standard of care, but going forwardB-I hate that phrase-Bthose two drugs would probably not be used in combination with maraviroc or efavirenz in the future. Is that correct?

DR. HENDRIX: Some people are still using them though I think tenofovir and emtricitabine is more widely used now. That would be probably more prescribed than zidovudine and lamivudine but some people are still using combivir. I don't know if I am answering the question.

DR. MURRAY: I think it is in fact in the treatment guidelines and what you suggested is true, but there is still a lot of use. Those who have done well on that, they will stay on that and not change unless there is some other reason to do so.

DR. STRADER: And would resistance then be a reason to do so, to switch from lamivudine-based background therapy to the other?

DR. MURRAY: No, I think it is more AZT tolerability issues and perhaps a better virologic response rate.

DR. HENDRIX: Dr. Pau?

DR. PAU: I think that kind of leads onto my question. According to the background information, clinicians were allowed to switch the NNRTI base due to tolerability or other reasons and I didn't see in any of the presentation how many patients among the different groups actually truly had switched and if that made a difference in terms of tolerability, as well as efficacy or resistance.

[Slide]

DR. MAYER: So, zidovudine and lamivudine was used as background therapy in the trial and patients who were experiencing intolerance but not virological failure could switch to an alternative background regimen. In those patients who actually did switch their background regimen response rates were slightly better on maraviroc than on efavirenz. If I could have E-239, please?

[Slide]

We also had some patients who switched to a tenofovir-containing regimen, a small number of patients, but there was evidence that those patients responded well to the combination of maraviroc plus a tenofovir-containing regimen as well as is seen in other trials using a

tenofovir-based background.

DR. HENDRIX: Dr. Van Dyke and then Dr. Roland and then Dr. Dixon.

DR. VAN DYKE: Getting back to the resistance issue, my concern about the 184 really is that it is a marker of incomplete viral suppression and I am just a little worried that maraviroc is not as potent an inhibitor, and whether it is due to unrecognized X4 virus in the minority population or whether it is bioavailability or a pharmacokinetic issue I don't know, but I think it is telling us something about breakthroughs because of lack of potency for whatever reason that we are not seeing in the other arm.

DR. HENDRIX: A follow-up to his comment, Dr. Havens?

DR. HAVENS: Well, yes, I agree with you completely so that would be like the unboosted atazanavir. It doesn't fail with atazanavir resistance; it fails with the 184. So, it is just a marker, a weak sister in the regimen.

On the other hand, as was pointed out already, the slide that they showed of when the efavirenz group came off therapy was quite early. So, the toxicity of the efavirenz

essentially protected you from seeing that. So, it is hard to balance those two out. I think that is why we are having a discussion.

Exactly right, that is one more thing that identifies that maraviroc in this context wasn't apparently as powerful, potent, at controlling plasma virus as the comparator agent or that the comparator agent wasn't kept on long enough to be able to show the same lack of potency and the development of resistance that is easy to get, which is a single step 184.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: Yes, two points. One small point, I just wanted to remind us that there were TAMs[?] also observed in both arms and I am not sure whether there was a statistically significant difference. It looks like there was 8 percent in the efavirenz group and 14 in the maraviroc group, but just not to blow off the 184 as an unimportant kind of issue.

But that wasn't actually what my comment was about. I want to think a little bit about this blip issue. So, you know, it was raised in the documents that we read, and I have to say it made a significant impression on me. I

notice that it was mentioned during the sponsor's presentation but it wasn't actually documented in the slides. So, I just want to think a little more about it.

So, what we have been told about it is that in the secondary primary efficacy analysis, the less than 50 copies at 96 weeks did not meet the non-inferiority outcome. However, 9 of 11 maraviroc patients with a detectable viral load apparently were undetectable at their next measure or at subsequent measures, and 2 of the efavirenz subjects were undetectable.

Now, that has had an influence on me and made me want to be more sympathetic and a little bit more generous in my thinking about whether this drug is more efficacious than the strict efficacy outcome would suggest. So, I am wondering has FDA or has the sponsor done an analysis of all of the outcomes, so the 48-week and 96-week 400 copies and 50 copies, not counting the last detectable viral load if the subsequent one was undetectable, if it was a blip.

Because if it hasn't been done for all of the outcomes, then I think we really just need to try as hard as we can to disregard being given that information for just one of the outcomes.

DR. MURRAY: We have ben struggling over this issue of whether to use what we call the snapshot or the time to loss of virologic failure, the TLOVR. The snapshot is an easier analysis for us to conduct and I think most people would kind of know what, you know, undetectable at this time point means versus time to loss of virologic response which, if you don't have a value for some reason at the time you are measuring for your primary endpoint, let's say at 96 weeks it is missing then, you know, you are called a failure and the TLOVR allows you to look beyond that to see if you are able to suppress.

So, I will ask our statisticians here by the TLOVR and our analysis did they, quote, meet the 10? The same as a snapshot? So, it was just a little below 10? Okay.

DR. ROLAND: I am not sure that the TLOVR analysis would fully address the blip issue with viral load measurement. It is a significant clinical issue for us. We don't really know what to make of a single detectable viral load followed by a series of undetectable viral loads. So, if we are calling a drug not efficacious based on what might be just a blip--

DR. MURRAY: Well, no, the TLOVR algorithm makes

you confirm so if you just have one above you don't count it as failure. You have to have two to be counted. So, that is why it differs a little from the snapshot. Now, when we looked at a lot of different trials and the snapshot and the TLOVR were within a couple percentage points usually it doesn't make much difference to us because it is only a couple of percentage points. But in this case, I mean, we are really focusing heavily on virologic failure so, you know, it is good to probably look at both. But in this analysis I guess it was very similar.

DR. ROLAND: So, just to confirm that, one outcome continued to not meet the non-inferiority requirement.

DR. ZENG: For the TLOVR and for the week-48 analysis we do have the follow-up data and we can look at the week 96 data. For week 96 data, we don't have follow-up data.

In terms of outcome, the results are very similar. The conclusions are the same. For the TLOVR less than 50, week 48B-wait a second for week 48 the PRISMA assay meets both less than 50. Week 48 and 96 both missed less than 10 percent. So that is same as the snapshot.

Also, we compared the difference between the

snapshot and also the TLOVR. The majority are the same. The only difference is that some of them in the snapshot analysis, just as in the PRISMA analysis, counted as a failure. In the TLOVR we counted it as just a one-time rebounder because the last-time rebounder in the snapshot counted as a failure. Sorry, it is complicated.

For the last-time, for example, for the snapshot, we only look at it within the window. If it is less than 50 we count it as a success. If it is above 50 we count it as a failure. But, for the TLOVR we need two consecutive to confirm. So, some subjects bounce up, some subjects bounce down. But the majority are different. And, like I say, the conclusions are the same. Just the snapshot, the 97.5 lower bound is a little bit lower than the TLOVR algorithm.

DR. MURRAY: Can I ask ourselves a question then? Did you use data beyond 96 weeks? I think Pfizer gets that it was under the 10 percent but we are truncating at 96 weeks? Is that the reason there is a difference?

DR. ZENG: In the submission we didn't receive data after 96 weeks.

DR. MURRAY: Pfizer can respond. I think they have longer-term data because it is an ongoing trial, out to

three to five years, so they had the benefit of using longer-term data beyond 96 weeks. So, that is why there is a little bit of difference.

Again, as I said, you know, the ten percent is a clinical judgment non-inferiority margin and we really didn't stress out too much about a couple of percentage points around that because it is more of an arbitrary clinical judgment type of margin.

DR. HENDRIX: Can I follow-up on that? I am sorry, go ahead. In fact, in fairness, you are free to ask anyone on your team a question in public.

DR. MAYER: I just wanted to address the TLOVR question. If you can just show slide 34, which Dr. Heera presented in his presentation this morning?

[Slide]

So, we did look again at the efficacy endpoint at 96 weeks. Obviously, the primary endpoint was at 48 weeks. We looked at the 96-week endpoint of less than 50 copies/ml. And, for the principal analysis the differences were 3.9 adjusted, with the lower confidence bound of -11.5. We then conducted the TLOVR analysis which required 2 consecutive values of greater than 50 copies/ml to be a non-

responder and saw a very similar result at 2 years between efavirenz and maraviroc.

As Dr. Heera presented this morning, the differences were because of somewhat more patients in the maraviroc arm at week 96 having single viral load results of more than 50 copies/ml, but the vast majority of those were suppressed on subsequent visits.

DR. HENDRIX: Dr. Dixon?

DR. DIXON: In the nature of a further clarification, the participants whose treatment was changed on the basis of side effects and were, thus, counted as failures in the primary analysis, was there any analysis done? Were the data available to look for biologic status in those even though they had discontinued their initial treatment assignment to get their virologic status at 48 or 96 weeks?

It seems to me that there is a variety of questions and this business with the composite endpoints, and Jim Neaton is one of the world's authorities on the problems associated with composite endpoints. But in this case it does seem like it would be possible to do an analysis just focused on the biology at these times,

regardless of what the treatment history has been by that time. And, I am just wondering if that was done and, if so, what did those data show.

DR. HENDRIX: Sponsor?

DR. MAYER: I would like to call Dr. Westby up to address the question, which is what happened to patients who discontinued due to adverse events in terms of their development of resistance mutations.

DR. WESTBY: If I could show slide V-33, please?

[Slide]

So, we did look at patients who discontinued in the efavirenz group due to adverse events because, as I presented, many of the patients discontinued early and there was this imbalance that we have been discussing.

So, in 17 patients that we followed up, 5 of these are shown here and you can see the time of the last dose, what mutations subsequently emerged, and the study day they emerged, and follow-up regimen if we have that information, and their outcome.

I think what you can see is that in all cases that are shown here. So, these are the 5 of the 17 that we were able to follow up. We did see resistance, predominantly

resistance to efavirenz, after study discontinuation. The bottom patient, it has to be noted, did go on to nevirapine at a later time point so that may explain the NNRTI resistance in that patient.

I think this is probably consistent with what we know about efavirenz, that efavirenz has a very, very long half-life and so at the time of failure you don't necessarily see the resistance but the resistance can appear at a later time point.

Also, referring to the question before about M184V, it has been well described in the literature that because of the half-life of efavirenz and the fitness of the K103 mutation, you actually can see that K103 mutation in more patients than seeing the M184V mutation in patients that take efavirenz and lamivudine, but that mutation may still exist. It is just that you don't see it because this virus is highly resistant to efavirenz and it is extremely fit. So, you know, these are the data we have on those patients.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: I think Dennis' question is a good one and I gather you just don't have a lot of the data. It gets

back to what Bob said earlier. What is being done here is not an intention-to-treat analysis. This is a non-treatment analysis that is being done. If you were going to do an intention-to-treat analysis you would measure the viral load on every single person, no matter what happened to them in terms of a change of treatment, at 48 weeks.

And, we don't have that data. So, we are limited in terms of evaluating that piece of it on its own. Likewise, we don't have safety data on serious adverse events after people stopped taking treatment. So, that limits our ability, in my mind, to say anything about feeling comfortable with the data we saw on cardiovascular disease and malignancies because I cannot comprehend why anybody could not conjure up an argument that a drug potentially could do something in terms of malignancy or progressive cardiovascular disease that may not manifest itself for a long time later. So, the fact that you don't measure it, you don't see it because it hasn't been measured possibly, as well as the sample size being small.

But I think the discussion has been very good because it has been very focused about it, and I think it boils down, in my mind, to how much weight you give to the

improved or the greater biologic efficacy for efavirenz, the best we can understand it, versus how much weight you give the adverse events you see on efavirenz, and that is kind of good because actually it forces a discussion.

My point earlier is that if all you do is focus on this outcome at 48 weeks and the non-inferiority bounds you lose all that focus because it obscures the whole picture.

DR. HENDRIX: Let me ask a question of the FDA which relates to the non-inferiority bounds as they are set up. The agency makes lots of decisions on lots of drugs with changing or adding indications in other products in similar settings and we don't get asked this, but how often does it happen that you would make a decision to change an indication when there is a drug that fails to meet, let's say clearly fails to meet without question, the non-inferiority bounds and, yet, it appears to be close enough or not different enough although it is truly different than what exists? That it is judged to be of value and gets a change in the label?

DR. MURRAY: Well, you know, I can't think off the top of my head how many times, you know, this is done. I think in the past we have approved drugs, a long time ago I

think some protease inhibitor comparisons that didn't meet non-inferiority bounds but we knew it was active. So, our non-inferiority bound in this case is much, much stricter than what you would need to show that it was better than placebo, that it was active.

I mean, I think there is no question that maraviroc has efficacy in this population and even in people who don't have R5 there is some efficacy because they had 40-some percent response rate and with combivir you would know you would have a 2 percent or a 1 percent response rate, if that.

So, in this case I think it all comes downB-I mean, whether it is above 10 or -10, to me doesn't mean so much as you are just taking all the information together and making kind of a risk/benefit decision on what you value as important.

Debbie is going to mention this but for a treatment-naive indication-Bthis is not treatment guidelinesB-it doesn't have to be the preferred regimen. It has to be a reasonable regimen. Is this a reasonable treatment regimen for a naive population and, you know, that is the standard. You know, it doesn't have to be the best

regimen. We will leave other groups to decide what is the best regimen.

DR. HENDRIX: But does FDA have interest in doing that? I don't know what you have regulatory authority to do. I mean, this is an example where you are sitting on top of the data. I mean, there will be other bodies, review bodies that make recommendations for what is first- and second-line, and so on, but you all typically don't do that but it might seem to be sort of the natural evolution of this sort of thing when you are sitting on the data and making these decisions.

DR. MURRAY: Well, it kind of becomes hard for us because as each drug gets approvedB-I mean, we have drugs already with indications in general for treatment of HIV and they were the standard. You know, nelfinavir was the standard at one time and, you know, we don't take away indications as new drugs come out. So, it is kind of hard for us, because we have an evolving field, to go back and, you know, pull indications from label. We generally don't do that.

So, I guess our preference has not been to rank order drugs in terms of real complex problem for us. It is

probably easier to address in guidelines which can change. You know, there is one document and it can be changed very much more quickly than us looking through every label and getting out anything kind of, you know, yes, this is no longer first-line but it might still be reasonable in a certain population.

DR. HENDRIX: Let me summarize the discussion so far. So, we had actually a lot on this, focusing on the differences and the direction of the resistance outcomes, parsed apart from the direction of the adverse event and discontinuation results.

A lot of discussion about the problems with the composite endpoints, especially when the results move in different directions with different elements that make up that composite.

Discussion about the resistance, sort of the future impact of resistance in the present weighed against the significance of adverse events. Within that discussion of adverse events, looking at differences in practice and in different locations within the study, and that kind of heterogeneity that gets added as well.

Then, looking at the differences in the

definitions of virologic endpoints in terms of the snapshot versus the TLOVR and considering the importance of those in making judgments about which of the virologic endpoints are useful to make decisions.

So, I will go ahead to the third questionB-I am sorry, Dr. Grant?

DR. GRANT: I think there was a key point made that shouldn't be overlooked, which is that the information that we want most we don't have, which is the prevalence of resistance at 48 weeks in everyone who was randomized, and the prevalence of virologic suppression at 48 weeks among everyone who was randomized.

We are carrying forward outcomes based on switches and failures but we really do need to know what they switched to and whether that was successful. We saw a little bit of data in subgroup analysis but the overall analysis we just don't have, which is at the end of a year, initiating an attempt with maraviroc, what do you get in terms of virologic suppression and resistance and initiating with efavirenz. No matter how you end up, what do you get? You know, I think that has implications for study design in the future, the importance of carrying forward the

observation for at least a year.

DR. HENDRIX: Thank you. Dr. Neaton?

DR. NEATON: Just one more thing that I might emphasize too, you know there are a lot of drugs where you are willing to give up some efficacy for improved safety, and vice versa possibly. It is for that reason that the other thing that worries me about a composite like this, not only things going in different directions, which may be almost anticipated, is that there are such different dimensions of kind of what the drug is doing in this case and what the evaluation is, and putting them all together may obscure something that is very important.

DR. HENDRIX: Thank you. Did you want to make a comment?

DR. MAYER: I just wanted to potentially show a slide that could be helpful in terms of the next regimen issue.

DR. HENDRIX: Okay.

DR. MAYER: So, if you could show slide E-19, please?

[Slide]

In this trial, and we have already presented some

of the data, we intended to be able to actually follow patients even after they went on a subsequent regimen, with the same visit schedule as patients who are on blinded study drug.

This shows the percentage of patients who achieved less than 50 copies/ml regardless of discontinuation, and includes people followed in study off drug on their next regimen. You can see that for week 48, which was the primary efficacy endpoint for this study, there are very similar results between maraviroc and efavirenz. Similarly, at week 96 also the results were similar numerically in the two treatment groups even accounting for patients who discontinued their blinded drug and went on a subsequent regimen.

As Dr. Westby showed versus Dr. Heera showed, patients who were largely followed on their subsequent were able to suppress on a follow-up regimen equally frequently between maraviroc and efavirenz. Even those patients that developed lamivudine resistance, those patients who developed that on maraviroc, were largely able to suppress on a subsequent regimen, keeping in mind that that actually occurred several years ago, before we had some of the newer

drugs that we have available today to treat drug resistant virus.

DR. HENDRIX: Leave it up, please, if you don't mind. So, the 311 and the 303, the reduced data set after using the more sensitive assay, in how many of those 614 patients did you have a measured viral load at 48 weeks? I can't tell from your slide how much is being imputed as failure versus how much is actually being measured.

DR. MAYER: So, how many people discontinued--

DR. HENDRIX: No, you are saying you are following the people that discontinued. That is great. I just want to know how many people at 48 weeks had a measured viral load contributing to this graph.

DR. MAYER: Can I have slide E-61, please?

[Slide]

This actually plots viral load less than 50 copies/ml for both efavirenz and maraviroc over 96 weeks, with the numbers that are contributing to those results at the bottom of the slide.

So, at week 48 it is 228 and 234 that are contributing to that result at week 48, and then 203 and 210 at week 96.

DR. HENDRIX: So, you are missing a lot of data at 48 weeks.

DR. MAYER: We are not. We are imputing discontinuations before--

DR. HENDRIX: But I thought your point was that you were following people through 48 weeks irrespective of discontinuation.

DR. MAYER: And that is what I showed. We didn't follow everyone, you know, because there were patients who were lost to follow-up, but we made an attempt to follow patients for as long as we could.

DR. HENDRIX: There is about a third where there is not virologic data.

We will move on to number three. Do you want to introduce this and after you introduce we vote and then we describe or justify our votes, Dr. Birnkrant?

DR. BIRNKRANT: As introduction to this question, I would like to split it out in what we are asking and what we are not asking. What we are asking in this question is a risk/benefit question. In other words, do the benefits outweigh the risks for use of maraviroc in this particular population? We are not asking you to answer, as Jeff

alluded to, whether this should be first-line therapy for naive subjects.

We can handle describing the clinical trials as well as the issues related to the outcome data, within the label under the indications section, by using bullets to highlight caveats with regard to interpretation of the data. So, that is a possibility. We can explain things further in the label. But, again, we are not asking about a vote on first-line therapy in particular.

DR. HENDRIX: First-line meaning preferred.

DR. BIRNKRANT: Preferred, right.

DR. HENDRIX: Which is different than treatment-naive first-line therapy. I have been corrected. We can have discussion on this before I ask you to vote so, please, discuss. Tracy, go ahead.

MS. SWAN: We have seen so little data on people with very low CD4 cell counts, and with so many people getting diagnosed at that point I just think this is a safety issue and we haven't seen that data. And, since maraviroc has an immune reconstitution benefit IRIS is a safety issue and I can't really say from what I have seen if people with low CD4 cell counts who are 5-tropic and

treatment-naive might be at greater risk of IRIS from using this drug.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: I want to hear from Dr. Neaton on the subject.

DR. NEATON: I think there is no question, if you ask the first question, does the drug have activity, it clearly does. So, that is what the FDA is interested in and they probably knew that answer before they brought it to panel.

From my point of view, it has inferior virologic efficacy and the thing I am concerned about, and it is a little bit the opposite of Tracy's question, if guidelines do get relaxed and this drug is easier to use among people with higher CD4 cell counts because there is less screening involved you are going to find more people that potentially make people eligible but I don't think we have a good risk/benefit kind of assessment from this trial. It is inadequate on its own.

So, I would like to see another study to reinforce kind of what we are seeing here among people with somewhat higher CD4 cell counts. I would like to see kind of the

study done perhaps with a different background nuc regimen which is kind of consistent with people are using today, and would like to see kind of data that kind of clearly tells us kind of what we are giving up in terms of loss of virologic suppression versus safety.

I think all the data we have today have to be kind of viewed with some caveats because it is nice that you tried to follow people after they discontinued, but you didn't. There were five to six percent lost to follow-up in the first year. There were lots of reasons for losing people for other reasons. All those kind of things, when you are trying to show that two drugs or two regimens in this are similar kind of work against that claim. Sloppiness almost makes it kind of easier.

So, I would like to kind of see the performance of the trial improved. So, my answer isB-you know, I would like to hear the other discussion, but from what I heard from you guys, the experts treating the patients, is that you tend to kind of weigh the virologic kind of failure and it was a worse situation than the safety and that would lead me to say no.

DR. HENDRIX: Dr. Grant?

DR. GRANT: You know, I would argue on the merits of having options. Especially in some subgroups it is important that we have agents which are pregnancy class B rather than C and D, and this is one that fits the bill there.

I think that it is a regimen that we see in these data evidence that it is better tolerated than efavirenz, and I think that that is important in practice, especially when you move away from highly sophisticated practices. So, I guess I would think that tolerability and safety are important.

The other issue, you know, that is very impressive in this data set is that the increments in CD4 counts are higher in the maraviroc arm. We have always wondered whether the CD4 count that appears in this setting represents functional immune reconstitution and I think there is a bit of data presented here that suggests that there is clinical benefit, and that is the TB rates. I believe there were nine cases in the efavirenz arm and just one in the maraviroc arm. I may or may not have got that right but it was clearly lopsided. So, I think that we are seeing a signal here that people can avoid TB if they can

enjoy a prompt CD4 benefit and maraviroc affords that.

I guess I agree with you, Jim. The evidence suggests that the efficacy in people who are actually able to take the two drugs might be less in the case of maraviroc. But as a total picture, it looked to me like people randomized to maraviroc did pretty well overall; that they were able to tolerate the therapy better; they avoided tuberculosis better. And, I think those are issues that matter a lot in my opinion.

DR. HENDRIX: Mr. Marco?

MR. MARCO: So, I am a bit conflicted I guess, just sort of with myself and where I am, whether it is as a patient advocate, patient educator, or, you know, somebody who has spent many years now studying clinical trials and becoming a fledgling epidemiologist, and knowing that I should pay attention to the primary endpoint and not, as Dr. Murray said, you know, we would like you to look at the 96-week, and I think we should look at the 96-week.

I think the 96-week data does not bode well for maraviroc, and I think the lack of viral suppression that we see and then the lamivudine mutation is, I think, pretty scary.

Then also, the small sample size. Dr. Neaton said that, you know, we are not able to see enough stuff. So, I almost feel like we are not able to tease out enough and almost being penalized for being asked to decide.

I know you should look at subgroup analyses, but as Dr. Grant just talked about the CD4s, I have issue with the baseline viral load and the people who had over 100,000 copies. It seems much less effective than efavirenz in those with over 100,000 copies. Over 100,000 copies is common in the community and I am afraid that this is, you know, maybe a TRIZIVIR-like drug. Under 100,000 fine, but not. So, those are my comments. I would just have to say no because the safety of efavirenz is not an issue and I am really more concerned about the lack of virologic suppression resistance.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: In terms of thinking about approving this, and in terms, I think, of the various different levels we should put our thoughts to, in terms of efficacy I agree with some of the comments already made. I am not convinced efficacy has been proven, comparable efficacy has been proven. I think the discontinuation rates were high.

You know, I think in some ways this trial is a victim to the time that it is being presented because a couple of years ago this would be attractive, but we are comparing it to efavirenz plus combivir. Even that, compared to studies that I have looked at of efavirenz plus truvada, efavirenz plus truvada is even that much better. So, we are comparing it to something that doesn't have as much efficacy as other regimens.

In terms of the immunologic data, yes, there is that CD4 rise that might be clinically important, as Dr. Grant pointed out, because of the TB rates. But if the percentages are not significantly different in terms of CD4 percent, I am just not so sure it is clinically important and I would want more data about that before hanging my hat on that as the reason to approve it.

Then, in terms of safety, I think the safety so far is looking okay, but in terms of niche groups or options for other people I am not convinced yet it is the right drug to be thinking about in terms of pregnancy because I just haven't seen enough data yet. So, I actually don't agree with that.

In terms of hepatitis C, there was only about five

percent of the patients who were viremic so, again, I think it is still an open question.

Then, on the other side of the coin is the resistance issue again. You know, I agree with the comment that not all resistance is created the same, however, you know, this issue about lamivudine causing some favorable profiles in terms of AZT, hyper susceptibility, etc. that has to do with replication capacity. We used to talk eons about that several years ago when we didn't have much else. Also, all of those advantages are in the setting of ongoing lamivudine pressure.

So, we don't do that anymore because we have many other options for treatment, and when you lose a drug like emtricitabine or lamivudine you have to switch to other regimens that have more pill burden and other toxicities, like AZT which caused the leading serious side effect in this trial, which was anemia.

So, I feel like there are a lot of promising aspects to this drug for naive populations but this trial doesn't convince me-Bthe number of discontinuations and the reanalysis; there are too few patients. I am just not convinced that it is equal and when we have other options

like protease inhibitors, which we haven't even spoken about, I am just saying there is an array of choices. It is not like five years ago.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Well, first of all, when we answer the question can we suggest a bullet, like Anot in pregnant women@ until there are adequate PK data? Or, would that be overstepping the bounds you would expect the committee to set for itself, Dr. Birnkrant?

DR. BIRNKRANT: Well, I am glad you brought that up because unless a trial is actually done in pregnant women claims can't be made, that is, advertising claims that a particular drug is appropriate for pregnant women.

What does category B actually mean? It either means that the animal studies didn't show any adverse effects but there are no studies in pregnant women, or it means that animal studies did show an adverse effect but there are studies in pregnant women that didn't show the effect.

So, in this case we have animal studies that didn't show an effect but we don't have any studies in pregnant women. So, the company could never claim that this

should be used in pregnant women given the data that we have at hand. If they conduct a study and it has favorable outcome, then that is a whole different issue.

So, as far as putting a bullet in the indications to warn against use in pregnant women, I don't think it would necessarily be handled that way but it could be handled in another section in the label that we now have describing what available data exists regarding use in pregnant women.

DR. HAVENS: It seems disingenuous to think that some of this wouldn't be coming up since the opening slides and the closing slides from the sponsor both had pregnant women on the slides. We have heard already here that people think it is easy to use for people who are naive. Many of the treatment-naive patients we might see who can't tolerate efavirenz are pregnant women. So, it is the natural slot for it.

Since there are no data showing even PK, let alone benefit, and since PK seems to be an issue here, a specific statement warning about its use in that otherwise easy target population might seem appropriate to some members of the committee. It sounds like you don't want us to mention

the bullet later so I guess I don't have to mention it later because I already brought it up.

The other question I had was from a virologist. Is there some sort of biological plausibility to the possibly lower benefit in clade C? Is there some biological reason for that? Who is best able to answer that question? It is an open question.

DR. MAYER: I can hand this over to Mike. I think that, you know, we haven't found any virologic reason for a lower response in clade C. We have extensive in vitro data showing activity of maraviroc against clade C, clade B and other clades, and we didn't see any evidence of more emergence of CXCR4-using virus in clade C infected patients in the study or of maraviroc resistance in those patients. So, we don't believe there is any virological plausibility for lower activity in clade C. Mike?

DR. WESTBY: There wasn't any virological imbalance, other than that fewer patients actually did switch to using CXCR4 in clade C, as has been described before. There was no increase in resistance or other factors. It is possible that it was poor adherence over time but we didn't see any virological reason.

DR. HENDRIX: Dr. Pau?

DR. PAU: I wanted to go back to the question about CD4. I echo and agree with everyone that has said that we don't really know what that CD4 increase really means. However, also this is not any different from the comparison between various protease inhibitors and efavirenz. Particularly, ACTG trials have shown that patients on Kaletra actually have a higher CD4 increase than on efavirenz. So, maybe that is a question about efavirenz and maybe this is not a right comparator for maraviroc in terms of the CD4 response. Whereas, when you compare it together with a PI-based regimen that may be actually shown to be fairly similar. If I remember correctly, the Kaletra responses are actually both CD4 percentage as well as absolute CD4 increase as well.

My other concern and, you know, being brought up in a middle class family, my main concern is always cost. I will consider that that is a consideration that we have to think about-Bnot we as a group here but I think obviously clinicians would have to think about that in the days when we recommend also using resistance testing prior to initiation of therapy, and on top of that using a test that

costs $2,000 before initiation of therapy is a consideration that some people might have to think about.

DR. HENDRIX: Dr. Dixon?

DR. DIXON: In myself I am sensing some discomfort in at some level changing the yardstick. The primary analysis that was agreed to in the protocol I believe does provide evidence that maraviroc in this combination is safe and effective. If we want to have a discussion about what appropriate endpoints the FDA ought to be demanding for studies of this type, I think that is a bit of a different discussion. Similarly, the question of whether one trial is sufficient, I think that is a different discussion at some level.

I am also disappointed that the virologic data at week 48 are not as complete as we would like them to be. Nevertheless, the study was designed with an endpoint which counted as failures discontinuation for side effects. Somehow I feel some obligation to stick with that agreement that was made at the design stage of the study.

I should say beyond that, the other points I think are all important points but I see them more as guiding the thinking for what study to do next rather than what to

conclude from this particular study. So, at the moment, pending further discussion by the panel, I would be inclined to support the application.

DR. HENDRIX: Dr. Veltri?

DR. VELTRI: Yes, along the same lines, I think it comes down a little bit, at least in my mind, to biologic plausibility activity. The drug is already approved in treatment-experienced. There are some virologic issues here which are unexplained. But this is not necessarily such a stretch, biologic stretch let's say if you are trying to show this drug prevented aortic stenosis. So, I think that has to be taken into consideration.

I think what Dr. Grant said is also important. Medicine is pretty much always regarding tradeoffs and options for both physicians and patients. Dr. Neaton made a point I think that sometimes there are tradeoffs even with drugs, for instance anti-phlebitics where someone comes in with an MI. You want to treat the ischemia but there may be a downside of bleeding and if the patient bleeds you have to stop the drug. The bleeding itself may be problematic but I think a choice between an MI and a two-unit pack red cell, you know, that has to be traded off as well and sometimes

they are related.

Finally, as Dr. Dixon was saying, I think the sponsor here was doing a contemporaneous trial at a time when X amount of information was known. There were prespecified endpoints, prespecified analyses. New assays came to bear and this was discussed with the FDA and the agency, and I think both in good faith and good, earnest attempts they tried to get the answers as best they can.

We are faced now with some data where there are some issues, but I believe that the drug should be given an opportunity based on the available data, that this is not that far of a stretch and that it is about tradeoffs and options.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: Yes, I am really glad we are having detailed discussion because I feel very ambivalent and I don't like the idea that at some point I have to push a button. So, I am going to think through some of the issues that are leaning me in the direction that I am leaning in.

I think the bottom line is that the FDA's job is to not decide, like you said before, whether this is the best drug but is this an acceptable drug for clinicians and

patients to be able to consider as an option. In that regard, the first thing that I think about is safety and I think it is really important to say in the label, if you do decide to approve this drug, that we don't know if this is a safe drug to use in the context of viral hepatitis, not based on the data that we have.

The second question is about efficacy. Clearly, it has effectiveness. I think we have a lot of questions and concerns about its relative efficacy and I think it is important that the label be clear about that, and clear about exactly what the resistance outcomes were and what the risks are of potential inferior efficacy to other available agents because clinicians and patients are going to need to weigh the risks and the benefits, and they need to know that these were the consequences.

I struggle a little bit around the issue of therapeutic drug levels. I know we will talk about therapeutic drug monitoring which I think is a completely different issue, but here I do think that the label should say something about there being quite a bit of variability in drug levels and uncertainty about what is contributing to that.

I do want to address the cost issue. I don't think that is FDA's job at all, but I run a public program and I have to think about that. So, the Ryan White legislation requires that there be one drug in every class of antiretrovirals on ADAP formularies. It is not clinically appropriate legislation but it is the legislation.

ADAPs across the country, if they aren't already bankrupt, are going bankrupt. So, I think that manufacturers of products, whether they be testing products or drug products, really need to understand the implications if this drug does get approved for this indication on public programs.

DR. MURRAY: I just want to comment on the cost issue. Since we are not allowed to do it, I guess we would prefer that you not consider that as much in your vote and stick more maybe to the kind of risk/benefit because we are really not supposed to consider, you know, cost when we make the regulatory decisions. It would be helpful for us to have that point kind of your vote as well.

DR. HENDRIX: So, I should instruct the jury to disregard the last comment.

DR. MURRAY: Well, no. No, it is important comment for people to consider but, I mean, we are not really supposed to have that as part of our regulatory decision.

DR. HENDRIX: The time has come. We are going to vote. We will be using this electronic voting system. Each member has three voting buttons on your microphone. I direct you to your microphone so you can see these. They are now flashing. There is a Ayes,@ a Ano,@ and an Aabstain.@

Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed their vote the vote will be locked in. The vote will then be displayed on the screen. That is always my favorite part, when you see your name and your vote.

I will read the vote. For those of you who have not been here before, so you will know, I 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, as well as the reason why they voted as they did.

I will just make a comment here in terms of time.

I think many of you have made comments. You certainly can make them again but you might edit those somewhat based on things you have already said. Okay? So, now we are ready to vote. So, if there is no further discussion on the question, and I don't see any other lights or hands, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the flashing button firmly after you have made your selection. The light will continue to flash. If you are unsure of your vote please press the corresponding button again. Go ahead and vote.

DR. TRAN: Go ahead and vote again, please.

[Electronic voting]

DR. HENDRIX: Do you have all votes registered now?

DR. TRAN: Yes.

DR. HENDRIX: Good. All the votes are registered. Thank you. The voting result, for the record, is yes 10, no four, abstain zero.

Now we will go around the room and if you would state your name for the record, your vote, and brief reason why you voted the way you did. Dr. Neaton, go ahead and

start.

DR. NEATON: I voted no for reasons that I pretty much already stated. I do think that the way the question was phrased, and I respect what Dennis had to say about the primary endpoint and I feel bad for the sponsor because by most measures they met that, but I think that you need to look at safety and efficacy separately.

I would be very concerned in a naive population going forward with potential loss of efficacy and not a good understanding of the adverse events. While the nine versus one TB cases were intriguing, we heard before they stopped collecting the data on TB and other adverse events after people went off therapy. So, we have on idea what the rates of these events was even in any kind of an intention-to-treat analysis. So, that was the reason for my vote.

MR. MARCO: I think also that I was, hopefully, pretty clear earlier but I think it was the lack of efficacy that I saw as far as its comparison to efavirenz. You know, I did look at the 96 weeks, I can't help it. Also, I don't think that side effects and discontinuation in the efavirenz arm really swayed me one way or the other. I didn't think it had a huge bearing.

DR. CARGILL: Yes, I voted yes even though I was incredibly conflicted, like my colleagues, about this because I felt that some of the guidance from the FDA helped assist me in that we are not looking for the absolute best but we are looking for an option. I continue to have some of the concerns that have been expressed but I also think this does expand our options.

DR. HENDRIX: Dr. Grant?

DR. GRANT: Yes, I think I stated why I voted yes. It is the safety profile that I think matters in first-line therapy, as it does later, especially given the long-term life expectations of people with HIV at this time.

I was impressed by the increase in CD4 count which may help, especially in populations that are facing an enormous TB epidemic. The lipid profile also I think indicated to me that maraviroc should be an option that could be considered.

But, clearly, my vote was based on the guidance that we are voting whether this should be an option rather than voting whether this should be the preferred first-line therapy. So, that guidance was pivotal in my voting.

DR. HENDRIX: Hendrix. I voted yes. I have to say

that I have continued to move toward ambivalence as the afternoon wore on, but I found it a very useful discussion. I think in the end I thought that the outcomes were a reasonable approximation of the way clinicians will make decisions if they have something useful in their own hands, weighing what appeared, after the fact now, to be clear virologic differences, although it is complicated to judge their future.

Also, if the subjects' adherence were better than it appears to be, it depends on how you look at the data but if patients take their drug their virologic outcomes are much better. So, that is, of course, a subset analysis but it appears that, you know, that would mitigate some of the differences as well.

The side effects I think are very important. As they occur subjects either can or cannot bear with them and they move on to something else if there is something available. And, having something available would be a benefit, like this. Likewise, there seemed to be clear benefits in terms of discontinuations and adverse effects that counterbalanced in a reasonably fair way, as I judged it, in favor of maraviroc.

So, sort of the composite decision in my own head was that it made sense to have this as an available option, and knowing also the FDA has the option of putting in specific caveats to be considered in terms of the application of this and the indication is also helpful as well.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: I suppose my vote of yes which I made is a measure of my trust that the FDA will help write the label to capture the tradeoffs that we have been discussing between efficacy and toxicity, to specifically link the use of this drug to a specific test that is required prior to its use, and to confirm their concern about issues related to its use in pregnancy.

DR. HENDRIX: Miss Swan?

MS. SWAN: I voted no, not for lack of trust in the agency, the guideline panels or other entities but because I simply wasn't overwhelmingly swayed by the efficacy data. And, I was thinking of the modern clinical environment that is not necessarily people who have time to read as much as they can; don't have adequate time with patients; and see people who see things in direct to consumer advertising who

also haven't read the fine print, and I was just concerned in that context. But I am looking forward to more data on this drug.

DR. HENDRIX: Dr. Pau?

DR. PAU: I voted yes, mainly because of what Jeff and Debbie said, as an option for individuals where there could be, you know, multiple other options or maybe, you know, there are no other options.

However, given that, I think the next question is going to be very important because I think a lot of postmarketing work needs to be done; a lot of research questions need to be answered, especially with a population that I don't think is the right population which was listed in the last slide for TB patients. I would not trust using maraviroc in patients with TB. Even the pharmacokinetics did not convince me. So, I think that we need to have more data and that is really critical.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: I voted yes for the reasons, and with the reluctance that I mentioned right before we voted, and my sincere hope is that FDA will be very, very careful and tough in your label and that will motivate the sponsor to

invest what will be very significant resources in doing more studies to convince us that concerns are not warranted and the label can be changed.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: I voted no, and I gave a lot of reasons earlier so, just to make it short, mainly because of my belief that we have several first-line options available to us in 2009. I am not convinced that this drug is my first choice for naive patients for the reasons I discussed. I think it is a very important drug and I also would like to actually commend again Pfizer for conducting that trial in those areas.

DR. HENDRIX: Dr. Van Dyke?

DR. VAN DYKE: I voted yes with some anxiety about this. I think clearly it has some benefits. The toxicity profile looks pretty good. It is clearly an active drug and it has demonstrated efficacy. I worry that it is not quite as potent as we would like it to be. I think there may be populations where it is less potent whether it is due to pharmacokinetics or what, and I think we need to know about that.

I guess in the end I was swayed by the fact that I

think if this drug is going to have a place it might actually be more effective with primary therapy than with salvage therapy because of the X4 resistance developing later on. So.

DR. HENDRIX: Dr. Dixon?

DR. DIXON: I voted yes for the reason that I expressed just a few minutes ago, that I think the evidence presented meets the standard of what was needed to support a yes vote, not withstanding all of the other questions that we can think of to address about this particular product.

DR. HENDRIX: Dr. Strader?

DR. STRADER: I voted yes because it appeared to me that the company made a good faith effort to reach the endpoints that they outlined in the protocol, and it seems to be safe and effective. I suspect that in the future medicine will be more of a targeted treatment as opposed to a blanket treatment and this appears to be a good drug for a specific group of patients, while realizing that it does tend to favor patients with a higher CD4 count.

DR. HENDRIX: Dr. Hagedorn?

DR. HAGEDORN: I voted yes because I thought it was important to have this option available for patients. It is

a drug with a different mechanism of action so having it available for first-line therapy I thought was an important option. There are some issues I think that need to be followed carefully, for example, the potential toxicity with anti-tuberculous drugs. That is my rationale.

DR. HENDRIX: Thank you. Let me ask the panel at this point-Bwe have two questions to go. We can either keep moving ahead and, as I look at these questions, a lot of the points that I think will come out in the fourth question have been introduced and may be a little bit shorter than if it were a totally fresh question, and the fifth perhaps as well.

Is your preference to take a break now for five or ten minutes, or do you want to just move ahead? I have 2:50. We have time in the schedule but I want to be sure that your endurance is up to snuff. Would you like to take a break? Let me just sort of look for shakes of heads. Okay, we will take a break for ten minutes. We will reconvene at 1500 hours.

[Brief recess]

DR. HENDRIX: We will reconvene. I am going to read the question. Question four, please comment on any

additional data that the sponsor should provide to further characterize the safety and efficacy profile of maraviroc in treatment-naive patients. So, background for the question, Dr. Birnkrant?

DR. BIRNKRANT: Based on the discussion that we have heard, there are obvious concerns about use in pregnant women, and we heard about use in patients with tuberculosis. But we would like you to elaborate the types of trials you would like to see in those groups in order for the label to be able to convey that type of information to practitioners. In addition, please comment on any other trials you would like to see conducted with this product.

DR. HENDRIX: Dr. Havens?

DR. HAVENS: Thank you. I note in the documentation from the sponsor that there is an 11 percent decrease in the C-average in people who eat compared to those in the fasted state, and 11 percent decrease in the C-average in a 20-year old compared to a 36-year old, and a 17 percent increase in the C-average in blacks compared to whites, and a 13 percent increase in the C-average in women compared to men.

So, if you were taking care of a young, white man

who eats the C-average might be actually substantially lower than the advertised C-average.

DR. HENDRIX: So, can you translate that into a recommendation, or may I do that for you?

DR. HAVENS: I would like to see it studied more completely, especially in younger populations, around the cusp of when people start to use it at age 18, you know, adolescents and young adults, especially since you have found what you consider to be a reasonable pharmacodynamic target.

DR. HENDRIX: If I can expand on that a little bit, I think in whatever studies are recommended, it is very much appreciated to have the sparse PK sampling that is provided there, but there is a huge amount of variability for there not to have been any of the differences that were described in some settings not to have occurred here. The huge difference that existsB-this will sort of get at the fifth question--with the fed and fasted profiles that were shown and then what went on in this trial, which not only split the difference but was skewed significantly on the low end. Some other way to get at that so there could be adequate information to make those kinds of exposure/response

relationships, especially if they could also adherence.

That is a thorny thing to get at but you need to have the combination of those two. You have to have some kind of adherence data, directly observed therapy, related data that will inform, PK data on the study to make sense out of what the adherence really looks like. It is hard to know what to do with it. The responses seem to be clear that they didn't happen when concentrations were low. So, that needs to be nested within whatever kind of study is done I think. It still could be a population PK-based approach but some attention to adherence measures perhaps in combination with that. Yes, a follow-up, Dr. Strader?

DR. STRADER: Yes, I just wanted to sort of echo that because I made a point earlier, or I was trying to make a point earlier about the 17 percent increased exposure among blacks and Aothers@ and 13 percent increased exposure among women. But when we look at the data it shows that they have a decreased response so somehow kind of reconciling the increased exposure decreased response. Whether that has to do with adherence or other things it is very important I think to look at in the future.

DR. HENDRIX: Dr. Cargill?

DR. CARGILL: Yes, I think that I would totally support that and ask whether it comes in the context of a phase 4 or whether we must or at least try very hard to take a look at these differences seriously between race and gender, as well as some of this reference to slow acetylators and other constructs. I know as I take off one hat and think of myself in the clinic, trying to make a decision about this, it just makes it very hard to decide without that information.

MS. SWAN: Coming as no surprise to anyone who heard my earlier comments, in people with lower CD4 cell counts with R5 tropic virus, even though guidelines are changing people are still presenting late and I think it is a really important population to have the data in.

There were some concerns among the community about the incidence and susceptibility and severity of tropic diseases and any disorder related to immune dysregulation both in treatment-experience and treatment-naive people. People are very keen to see a database with this information being collected with a safer or similar period as was with treatment-experienced people when it was approved, which I believe was five years.

DR. HENDRIX: Dr. Pau?

DR. PAU: With regards to what type of postmarketingB-actually, it is postmarketing already but other additional data, I would really like to see comparison with other types of first-line regimens, particularly maybe with boosted PI or a raltegravir-based regimen, as well as nuc-sparing regimen, and I understand there is an ongoing study right now.

I think that for the FDA, we really need to have not any more Ame too@ one drug plus NNRTI as initial therapy anymore. We need to find other ways to treat patients and get rid of NRTIs in some of the regimens. So, you know, I think looking at future naive studies there should be some kind of standardization as to how to go about doing studies that do not include nucleoside analogs as well.

With regards to the question about TB, I think that there need to be some ways to look at both toxicity, especially after hearing about the case of liver transplant that is associated with either INHIBITOR use together with maraviroc, whether this component associated with acetaminophen or not. So, any long-term safety study to look at combination of maraviroc with anti-TB medications

which would be hepatotoxic, as well as efficacy data from a virological efficacy standpoint, whether the 600 mg twice a day is recommended by the current labeling is the appropriate amount of drug to use, and whether there is in this case a role of therapeutic drug monitoring if you are using it together with rifampin or even rifabutin.

DR. HENDRIX: Dr. Roland?

DR. ROLAND: I would like to see a safety evaluation of the drug in the context of viral hepatitis.

DR. HENDRIX: Mr. Marco?

MR. MARCO: I think, similar to what Tracy had mentioned about seeing this in patients with lower CD4 cell counts, I also am going back to harp on patients with increased viral load and whether you can do a large enough study so that you can really parse out a treatment effect on viral load that is high, above 100,000 or low, under 100,000.

And, I don't know, some way to also power it enough to have enough different racial groups to see if anything is going on from the noise, I say noise that I see in the 96-week data.

DR. HENDRIX: Dr. Hagedorn?

DR. HAGEDORN: I just wanted to add regarding the viral hepatitis, that should include B and C co-infected groups. I think that is an important question.

DR. HENDRIX: Dr. Neaton?

DR. NEATON: This is perhaps a more general comment, but it seems to me--and this is not maraviroc--that the FDA needs to think about what the criteria are for these kind of decisions on naive populations and the thresholds for kind of giving them a label in this regard. My own bias is that the threshold should be way higher than what it currently is, both in terms of documenting, kind of with enough patients, the absence of really serious adverse events and virologic efficacy in kind of a design mode which kind of is better both in terms of being adherent to more general clinical trial principles and with better outcomes.

DR. HENDRIX: Are there other comments on the question? Dr. Pau?

DR. PAU: Just to follow-up with Jim's question and, you know, more for Jeff and Debbie, my understanding is that the number in this trial is not that much different from the other trials that had been approved for naive

populations. Around the range of between 200, 300, up to 400 patients for each arm had been used in most of the studies. Is that correct?

DR. MURRAY: That is correct, about 600-700 patients for naive studies is the norm.

DR. NEATON: I realize that and they should be five or six times that.

DR. HENDRIX: So, let me summarize. The question was to comment on any additional data that the sponsor should provide to further characterize safety and efficacy in treatment-naive patients.

I will just sort of run down the list of things, additional pharmacokinetic or concentration data to look at concentration responses; also adherence, perhaps in the same context; specific populations beyond black; data sufficient to assess exposure response differences; lower CD4 count populations; comparison with other regimens, specifically compared to different PIs and also with non-NNRTI-including regimens; the importance of data in the setting of TB; and drug interactions; co-infection with hepatitis B and C; additional data at 96 weeks sufficient to decrease the noise and parse out the differential effects; and increased

thresholds and improved standards, in fact, in general trial design to improve the sensitivity, to sort out the differences that might exist.

We will go on to the final question to discuss the maraviroc exposure-response data and whether the magnitude of benefit justifies exploration of therapeutic drug monitoring. FDA background on that?

DR. BIRNKRANT: No.

DR. HENDRIX: So, I will open it up for comments then. Dr. Strader?

DR. STRADER: Well, I think we don't know this information so it would be good to have studies to see whether or not therapeutic drug monitoring would be a beneficial thing. Of course, I think, as a clinician, we are always interested in making sure that we are treating the patients who would best benefit; that we are not continuing to treat patients who would not show any benefit at all. So, if there is any ability to show that there is a correlation between exposure and response and to monitor through time, it would be a good thing.

DR. HENDRIX: Dr. Pau?

DR. PAU: So, the data that you showed was C-

average and for the clinician out there it will not be easily done and interpreted by doing a C-average in most circumstances, and if there is a way of doing therapeutic drug monitoring I think there would be some guidance for the clinician out there as to what is the best time to draw the levels and how to interpret the levels.

DR. HENDRIX: If I could just add to that, I think it was very helpful to see the two examples of the fits and one of the fits was the sparse sampling, quite a reasonable fit. It looked as good as any population PK fit looks. The other example, which was chosen because it was extreme, was a disaster. I mean, you can draw a line through the middle of any set of data.

I think if there is a different kind of more sampling, I mean it is always more. We have added a lot of things to this, but having more of that kind of data would be very helpful, especially because it appears that the responses are so dramatically influenced by the levels that it is worth getting additional information.

I think the reassuring thing perhaps is that the C-average is going to be correlated with the peak; will be correlated with the trough and it will all be the same thing

because they are all based on the same model fit. But those model fits with such a highly variable kinetics, that is problematic so looking also at the actual data, if there is a way to do that, will be helpful.

Doing designs with concentration controlled studies, or at least building in specific targets, and there are excellent examples of what the targets would be here based on the analyses that were done here. So, I think those are very useful to design that study.

My sense is, especially in face of the suggestion of poor adherence data that was there, which is something I mentioned a little bit before, but I think the argument that the sponsor made trying to parse out what was an adherence issue was useful, to look at that, and I am not sure what the other variables would be that would describe that additional variation compared to other settings where it might have been more observed treatment and a better behaved kinetic profile.

But these adherence measures aren't in whatever kind of study you are doing. I mean, there are lots of poor adherence measures. Some are better than others and, hopefully, this is an evolving science but adherence has to

be part of it to make any sense out of the concentration data, again, because of the variability in both adherence and the concentration data.

So, I think it is critical to take this information and design studies, at least nested studies within whatever other studies will occur to make some sense out of this.

This is true, of course, for every antiretroviral that is out there. I mean, there are very few where we have any idea what kind of concentrations are desired. We have an idea of what concentrations are typical and associated with good responses. This drug is different in a lot of ways because it really falls off very quickly. There is clearly a very active part of the dose-response curve, it appears based on the data. So, this is going to be a very important part to fill out. Dr. Van Dyke?

DR. VAN DYKE: Yes, just to follow up on that, I agree, it looks like we have a pretty good idea what an effective level is here based on that exposure-response curve. To me, it sort of looks like the bell shaped curve of the bioavailability, ignoring adherence for a minute, was sort of sitting right on the edge of that in terms of

efficacy, and is the dose too low or do we just need to make sure that everybody is achieving a therapeutic level? Because it looks like, you know, there is ten percent of people that are not getting enough dose to suppress viral replication and it is a pretty fine edge, I think, where we are living on with this drug.

So, when I first read through that I like very much the FDA's approach to this where they said, well, let's just say we double the dose in that ten percent and see how much we improve, and those were remarkable improvements in that experiment.

Until I saw the information about all the adherence issues, you know, if these half of these failures were because they weren't taking the drug you could quadruple the dose and it wouldn't do anything for you, and occasionally they would actually take it and then you would be in trouble perhaps. So, it is very complicated.

That is why I think you have to sort those two things out. But it may be very simple, especially because the side effect profile is so good. You know, just nudging this thing up or knowing how to nudge it up, if there were a way to identify folks that are at risk of being on the low

end.

I think the multivariate analyses done to look at subsets didn't show anything. Again, I think the adherence thing, if there were a way to put that in as a variable, that might answer the question and that gives you an entirely different response to the thing in terms of how clinicians can work to change that.

DR. HENDRIX: Dr. McGovern?

DR. McGOVERN: You know, one thing too when I was looking at the old data on the treatment-experienced patients, it was so interesting, and this has nothing to do with levels but it is just like inferring efficacy, when you look at the Q daily dosing of maraviroc and the twice daily dosing in the experience trial, those viral load declines are almost identical.

So, it made a lot of sense that they should try this drug QD and BID in naive patients. The QD drug dosing arm, obviously, was discontinued because of lack of efficacy. Why was it so off the mark? It makes me wonder if maraviroc against a phenotypically changed virus might be somewhat different than maraviroc against a very fit virus.

DR. HENDRIX: I will respond a little bit to that

because I see people behind me shaking their heads. It was striking to me when the data were shown with the similar reanalysis with the exclusion of those subjects, I mean, numerically I think it might have been significant but it was not far outside the inferiority bound. That was really striking. I don't know if there was a larger number of those subjects that also happened to be, you know, dual/mixed or X4 at the beginning that weren't picked up.

So, it diminished a lot of those things and, with that, it made it look very much like the treatment-experienced data. When we saw the treatment-experience data the first time around I am only sorry that I can't make a stronger case for TDM this time because I thought it was a perfect case for TDM now.

There weren't the same kind of concerns with adherence issues, just because I think there wasn't data to suggest that that was an important variable, but it likely was there as well. But I think this is a very rich area. It wouldn't take an awful lot to sort through this. But I agree with you, it is very important. Dr. Havens?

DR. HAVENS: So, I would be interested to hear from the company what they consider to be the drug exposure that

would act as the most important pharmacodynamic target. Do they agree with the FDA? I think somewhere I read that you guys felt like a C-min of 25 was the target.

Then, was the treatment-experienced study reanalyzed using the extra sensitive Trofile or not?

DR. MAYER: Thanks for the question. Taking your second question first, we haven't reanalyzed the treatment-experienced data with the enhanced sensitivity assay.

In terms of our approach in terms of the C-average that best correlates with efficacy, I would like to call up Lynn McFadyen who is the pharmacometrics antiviral lead at Pfizer.

DR. MCFADYEN: Thank you. If I can ask for projection of slide CP-8 first?

[Slide]

When we are talking about the BLQ values we took that, as Mike Westby said, as a hard endpoint for lack of adherence. What you are looking at here is the maraviroc concentrations versus time off the dose for the patients in our monotherapy study. So, that was a patient study and you are looking at the multiple dose pharmacokinetics here.

You can see that down to 50 mg BID you can easily

measure concentrations out to 48 hours. Therefore, if we see BLQ values in patients, these patients have been missing at least three doses. We don't know how many. If I can move then to slide CP-40?

[Slide]

This is the predicted probability of success on the Y axis versus the C-average, and in the bulk of the patients you can see that the predicted C-averages are actually in quite a tight range. But the patients that are contributing to the exposure-response, around about ten percent of patients in the tail that Mike Westby mentioned earlier this morning are to the left-hand side of the green curve, and we marked all patients who had at least one BLQ in red. You can see the bulk of those patients fall to the left of the green curve.

So, we believe that adherence is actually the key factor here, and it is not just a little bit of poor adherence, missing a dose here or there. These patients are taking extended days off all their treatment. If I can go to CP-56, please?

[Slide]

On the left-hand side you see the same exposure-

response that you have seen in the FDA's presentation. On the right-hand side you can see the exposure-response analysis now after the removal of the BLQ patients.

Our conclusion from that is that it is not the C-average per se; it is the lack of adherence that is the key factor here. We don't know why they are poorly adherent but that is what the problem is here, and it is a problem will all drugs and the whole regimen. It is a patient problem more than a particular drug problem.

If I can hand over to Mike Westby to look at a couple of individual patients who didn't have a BLQ but had virological failure with no mutations, he can fill you in on what is happening there.

DR. STRADER: I just wanted to ask a question about the slide. On the left-hand panel it looks like there was a very sharp cutoff at whatever that number was, 65 or something, and then it seems to plateau for a while and then went up just a little bit but not very much, suggesting that the C-average is probably not necessarily the metric to look at but it is the BLQ. Is that what you are suggesting?

DR. MCFADYEN: Yes, it is poor adherence feeding into the C-average that is driving the exposure-response

relationship that was identified, and if you remove the patients with BLQ there is no longer a statistical relationship with success but the C-average.

DR. STRADER: So, as clinicians then looking at a C-average is something that probably would not be as helpful as making sure that patients are adherent by looking at BLQ.

DR. MCFADYEN: Yes, it is compliance that is the issue here.

DR. HENDRIX: Any other comments on this question? So, just to summarize then, the question was about the exposure-response rate and whether the magnitude of benefit would justify exploration of TDM.

There were a lot of comments that it would be additionally useful to look at that. There was discussion on whether the C-average or some other parameter that would be more useful to clinicians would be appropriate if the question was about whether TDM was appropriate or not because C-average is not something that clinicians are going to be using as a TDM decision point.

That is the end of number five so I will turn it over to the Division. I want to be sure that you have your last words, and I want to be sure that you have what you

wanted from the committee given the charge in these five areas, you know, while we are captive and awake. We are still yours for a few moments.

DR. BIRNKRANT: I appreciate that. Well, I want to thank everyone for their participation. I thought that the discussion today was quite useful and I am sure the company found it quite useful as well. We will take the comments back to the agency and use them to guide us in our regulatory decision.

Again, I want to thank everyone for your help, guidance, participation and comments, your outreach to the community, etc. Thank you very much.

DR. HENDRIX: Thanks, everybody. We are adjourned.

[Whereupon, at 3:30 p.m., the proceedings were adjourned]

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