AT

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 Kennedy Ballroom
Crowne Plaza Hotel
8777 Georgia Avenue
Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. PAXTON: I would like to welcome you all to this meeting of the Antiviral Drugs Advisory Committee. My name is Dr. Lynn Paxton. I am from the Centers for Disease Control and Prevention.

Today we are going to be discussing the new drug application 22-128 for maraviroc. I am just going to start off by saying that we are going to be adhering very strictly to the agenda and to the time so I hope that you will all keep watch on your time or, if not, I will. I would ask you all to hold your questions until after the FDA discussions. Unless you have some burning need for clarification, you know, just call for my attention but we are going to try and hold all questions until after that discussion.

I would also ask you to turn off all your electronic devices, including your blackberries. Even for people like me who are complete blackberry addicts, it turns out that it interferes with the electronic communications here and the

transcription. So, please turn off your blackberries.

I am also going to go ahead and ask that the committee introduces itself, and I think we will start off at that end of the table with Dr. Maribel Rodriguez-Torres. So, if you could each give your name and your affiliation, we would be appreciative.

DR. RODRIGUEZ-TORRES: Good morning, Dr. Maribel Rodriguez-Torres, Fundacion de Investigacion de Diego Santurce, Puerto Rico.

DR. YARCHOAN: I am Bob Yarchoan, from the National Cancer Institute in Bethesda, Maryland.

DR. WEISS SMITH: Sheila Weiss Smith, from University of Maryland.

MS. DEE: Lynda Dee, from AIDS Action Baltimore and the AIDS Treatment Activist Coalition.

DR. McGOWAN: Ian McGowan, David Guthrum School of Medicine at UCLA, Los Angeles.

DR. HENDRIX: Craig Hendrix, Johns Hopkins University in Baltimore.

DR. GRANT: Robert Grant, Gladstone and the University of California, San Francisco.

DR. GILBERT: Cynthia Gilbert, VA Medical Center in Washington, D.C. and George Washington University.

DR. ALEXANDER: Barbara Alexander, from Duke University in Durham, North Carolina.

DR. PAXTON: Once again, Lynn Paxton, CDC. And, can I remind you to please turn off your microphones when you have finished? It will cut down on the echos.

DR. REESE: Cicely Reese, designated federal officer.

DR. HAVENS: Peter Havens, Medical College of Wisconsin in Milwaukee.

DR. ANDERSON: Janet Andersen, Harvard University School of Public Health.

DR. NAEGER: Lisa Naeger, FDA.

DR. JADHAV: Pravin Jadhav, Pharmacometrics, Clinical Pharmacology.

DR. PROESTEL: Scott Proestel, Medical Officer, FDA Antiviral Products.

DR. LAESSIG: Katie Laessig, Medical Team Leader, Antiviral Products.

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

DR. COX: Ed Cox, Acting Director of the Office of Antimicrobial Products, FDA.

DR. PAXTON: Thanks very much. I have to read a prepared statement here so, in the interest of the Federal Advisory Committee Act and its Sunshine Amendment, we ask that the committee restrict their conversation of this topic to the open form of the meeting. We also ask the public and media to respect this process and hold their questions for the committee until the conclusion of the meeting.

Now I am going to pass over to Cicely to talk about conflict of interest and other matters.

Conflict of Interest Statement

DR. REESE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the

submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exception:

In accordance with 18 USC Section 208(b)(3), a full waiver has been granted to Dr. Barbara Alexander for unrelated speaking for the sponsor, for which she receives less than $10,001 per year.

Waiver documents are available at the FDA's docket web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the

agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We would also like to note that Dr. Eugene Sun was invited to participate as a non-voting industry representative, acting on behalf of regulated industry, but had to cancel his participation today and there was not sufficient time to arrange for the participation of an alternative industry representative.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. PAXTON: Thanks very much, Cicely. We are going to proceed now to the FDA's introductory remarks so Dr. Katie Laessig will be taking care of that.

FDA Introductory Remarks

DR. LAESSIG: Good morning.

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On behalf of the Division, I would like to welcome the members and consultants of the committee, colleagues from Pfizer and the audience to our meeting today to discuss NDA 22-128 for maraviroc 150 mg and 300 mg tablets that has been submitted by Pfizer with the proposed indication of treatment of adults with CCR5-tropic treatment-experienced HIV infection.

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You may be wondering why we have convened this meeting today considering that this is hardly the first antiretroviral agent to be reviewed. However, given the availability of the safe and effective agents, resistance and tolerability remain problems for many patients.

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Fortunately, drug development continues in the established classes of reverse transcriptase and protease inhibitors, as well as in new classes of integrase and entry inhibitors.

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That is why we are particularly excited to be here today to hear about maraviroc, a new antiretroviral agent known as a CCR5 co-receptor antagonist that targets a host protein instead of the virus directly. At the center of this NDA are two Phase 3 pivotal trials, studies 1027 and 1028, which are double-blind, placebo-controlled Phase 3 studies in treatment-experienced subjects with CCR5-topic HIV-1 infection. Supportive data is provided by Phase 2 studies, two 10-day monotherapy studies, 1007 and 1015, as well as a Phase 2b study, 1029, which was a 24-week study in dual- and mixed-tropic HIV-1 infections. We requested this study because at the time the development program was being considered we were unclear as to the relevance of the tropism assay and whether there could potentially be any treatment effect at all in these subjects or potential for adverse effects. In addition, there is an ongoing Phase 3 study in treatment-naive subjects. However, because the primary efficacy analysis in that study is at week 48, it is not part of this application

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Following the presentation by Pfizer, we will have an FDA presentation. I would like everyone to bear in mind that we are only at the end of the fourth month of the review cycle and, therefore, these FDA analyses and conclusions are preliminary and may be subject to change by the time any action is taken. That being said, we will cover a brief discussion of clinical efficacy, a more in depth discussion of safety, particularly issues that have surrounded this class of drug products including hepatic events, risk of infection and malignancy, QT prolongation and other cardiovascular events, creatinine kinase elevations and others. In addition, we will have a discussion of exposure-response modeling and the relationship of pharmacokinetic and other parameters to outcome. Finally, we will have a discussion of resistance and tropism which is a unique feature of this drug class, in particular tropism switching.

Many of these issues have been discussed in the FDA background and in the accompanying draft

document from the FDA forum meeting that was held last May. As you will hear today, we have some up to date information to share with you.

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Following the presentations and a break for lunch, and then an open public hearing, we will move to the questions and issues for committee discussion. These are, as outlined on the slide, regarding the adequacy of the evidence for safety and activity. Are there any gaps in the data or other needed information? Discussion of the safety areas of interest, hepatic events, malignancies, infections and others, as well as the tropism switching. We will also request a discussion of the adequacy of the data supporting the proposed dosing and what the committee feels might be the potential uses of tropism assays in clinical practice. Lastly, for extra credit, we will request the committee discuss the impact of maraviroc on the design of future antiretroviral Phase 3 clinical trials for treatment-experienced subject.

I would like to make one comment about the assay that was used. This was a critical aspect of the studies and at this time FDA is further considering its role in regulating this type of assay, however, Pfizer is committed to making sure this assay is available for clinical use.

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Finally, I would like to acknowledge the tireless efforts of the review team who managed to review the NDA, pull together their analyses and conclusions and make it available for presentation to you today, all in the four-month time period which borders to a "mission impossible" and for that we thank them.

Now I would like to invite Dr. Dunne to come to the podium.

Applicant Presentation

Introduction, Background and Overview of Maraviroc

DR. DUNNE: Good morning, everyone. My name is Mike Dunne. I am the therapeutic area head of development for infectious diseases at Pfizer.

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We will be presenting data this morning that supports the registration of maraviroc, the first CCR5 antagonist to be considered as therapy for treatment-experienced patients infected with CCR5-tropic HIV-1.

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I will start off our presentations with some background on CCR5 and its role in HIV infection, followed by an overview of maraviroc preclinical and clinical pharmacology findings. Dr. Howie Mayer, the global clinical leader, will present the Phase 3 efficacy results. Dr. Steven Felstead, the maraviroc team leader, will summarize the safety data, and Dr. Mike Westby, the virology team leader, will then review the in vitro and in vivo data regarding tropism and resistance. Dr. Daniel Kuritzkes, from Boston, will provide a perspective on medical need and maraviroc's place in the HIV armamentarium. I will conclude the sponsor's presentation with a review of the risk management plan and dose recommendations.

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The data presented this morning are provided in support of a claim that maraviroc, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with HIV-1.

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While many antiretroviral agents have been reviewed and approved by this committee and the division, there are some important features in this data review to bear in mind.

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The chemotype, the actual molecule, is from a novel chemical class so extrapolations from other compounds may not be feasible. The antiviral target is a human receptor, and not just any receptor but one which may mediate the immune response. While immune-related outcomes should be examined for their potential relationship to the binding of maraviroc to this receptor, we shouldn't forget that suppression of HIV viral replication itself also has the potential to significantly affect immune function. Lastly, resistance to

therapy needs to be considered differently as the inherent tropism of HIV potentially selects for a second pathway of altered receptability.

As a result, it is our belief that most integrated bases upon which to generate a risk/benefit assessment will be derived from clinical data collected from trials in the target population, and for that reason we have chosen to focus our presentation this morning on our two pivotal studies.

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First then, a review of chemokine receptors and HIV cell entry.

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In 1996, Feng, et al. published a paper describing the finding that a molecule they called Fuzeon, now known as CXCR4, was required as a cofactor for entry of a specific isolate of HIV into cells.

A few months later a paper was published showing that among a cohort of HIV seropositive patients 89 percent were found to have two copies

of the CCR5 gene and 11 percent had only one copy. No patient homozygous for the mutation of the CCR5 gene, called delta 32, was found to be seropositive for HIV.

Subsequent studies have found that these individuals, about one percent of the Caucasian population, by and large are perfectly normal in other aspects, raising the possibility that inhibition of the CCR5 receptor could offer a new target to treat HIV infection.

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Building on this finding, other studies have demonstrated that HIV-positive patients, heterozygous for the CCR5 delta 32 gene, have slower progression to AIDS and death, and one such paper is described here. In this nested case-control study among 343 men with HIV-1 infection, those with the heterozygous CCR5 genotype showed a highly significant prolonged duration of AIDS-free survival compared with carriers of the wild type genotype, shown on the left-hand panel. The mortality analysis also

showed a significantly prolonged time to death for the CCR5 delta 32 heterozygotes compared with CCR5 wild type carriers, as shown in the right-hand figure.

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How does a co-receptor actually enable entry of HIV into a cell? The entry of HIV into CD4-expressing cells can be divided into three discrete sequential steps. First, the attachment of the viral glycoprotein 120 to the CD4 receptor leads to a subtle confirmational change in gp120 itself. These changes expose structural elements on the V3 loop which then bind to a co-receptor, either CCR5 or CXCR4. This, in turn, induces a structural rearrangement in gp41 which is then able to insert a hydrophobic Fuzeon peptide region into the target cell membrane. This brings the virus and the cell membrane into close apposition to initiate Fuzeon and ultimately entry of the viral core into the target cell.

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So, where does maraviroc fit in? To

answer that question we will focus on the CCR5 receptor within the cell membrane. In this ribbon diagram the CCR5 molecule is embedded within the cell membrane. HIV-1 gp120 binds to the extracellular domain. CCR5 antagonists are allosteric inhibitors. They do not directly block the interaction between CCR5 and gp120. Instead, they bind to a pocket in the transmembrane region of CCR5. It is proposed that this causes confirmational changes in CCR5 that alter the shape of the extracellular domain such that gp120 is no longer able to bind.

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We can use this principle of cell entry to assay individual virus for the selectivity for the CCR5 or CXCR4 receptor or both. To perform this assay envelope sequences are inserted into an HIV expression vector. This vector is transfected into a cell along with a reporter construct containing the luciferase gene, here, into that cell. Within this cell these vectors will recombine to produce a pseudo virus which will subsequently be exposed to

a CD4 positive cell that has either a CCR5 or CXCR4 receptor on its surface. A virus population composed only of CCR5-tropic viruses will only produce a luciferase signal on cells carrying CCR5. This virus population can be classified as CCR5-tropic or R5 virus.

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Dual-tropic viruses are able to use CCR5 and CXCR4 as co-receptors for entry into CD4 positive t-cells. A virus population composed entirely of dual-tropic viruses will produce a luciferase signal on cells carrying CCR5 and on cells carrying CSCR4.

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However, exactly the same result will also be obtained with a mixture of CCR5-tropic and CSCR4-tropic viruses. Thus, when a bulk virus population is tested a positive signal on both CCR5- and CSCR4-expressing cells can indicate either a dual-tropic virus population or a mixture of CCR5- and CSCR4-tropic viruses. This is frequently abbreviated as dual- or mixed-tropic

virus. To differentiate between these alternatives large numbers of individual viral clones would need to be tested.

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With that overview of the test, let's review some terminology regarding tropism. It is important to be able to understand the rest of the presentation we will be doing this morning. R5-tropic viruses are identified when only CCR5-tropic virus is detected in the assay. X4-tropic virus is identified when only CXCR4-tropic virus is detected in the assay. And, dual- or mixed-tropic virus describes the situation in which either a mixture or CCR5 and CXCR4-tropic virus or a dual-tropic virus is detected in the assay.

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Using results from this Trofile assay, data from a number of clinical cohort studies illustrates that HIV-1 is predominantly CCR5-tropic in treatment-naive patients, with essentially no CXCR4-tropic virus. You can see that here. In

treatment-experienced patients we see an increase in X4 virus which is almost entirely due to an increase in dual- or mixed-tropic virus on this assay. Pure X4 tropism remains rare. Of note, even in treatment-experienced patients approximately 50 percent of those patients continue to have only R5 virus. You see that here.

Correlation has been observed between the development of dual- or mixed-tropic virus and lower CD4 counts, frequently seen in treatment-experienced patients. Whether CXCR4 virus is a cause of the reduction of CD4 or whether the reduction in CD4 allows for the overgrowth of CXCR4 virus remains unclear.

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So, now we move on to maraviroc.

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Maraviroc demonstrates selective reversible binding to the CCR5 receptor with an offset rate of 16 hours at room temperature. It antagonizes the binding of endogenous ligands of NIP 1-alpha, NIP 1-beta and RANTES, which shows no

agonist activity. It is active against HIV-1 resistance to current classes of antiretrovirals but not CXCR4-using virus. And, serial passage experiments demonstrate the slow emergence of R5 resistant isolates. It has excellent cross-clade potency against primary CCR5-tropic isolates and it has an antiviral IC_{90} of approximately 2 nM against primary isolates in peripheral blood mononuclear cells.

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Maraviroc has non-linear kinetics at low doses. At doses greater than 100 mg absorption becomes more proportionate to dose. Maraviroc is found to be widely distributed in rat autoradiography studies, especially into lymph nodes. CSF concentrations in the rats were 10 percent of plasma concentrations.

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Maraviroc is a substrate for CYP3A4. It has no effect on other cytochrome p450 pathways and is neither an inducer nor an inhibitor. Maraviroc has no effect on the metabolism of other drugs.

Maraviroc is a p-glycoprotein substrate. Excretion is mainly fecal. Two metabolites found in plasma have been characterized and found to have no relevant activity at the CCR5 co-receptor or any other receptors.

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Pharmacokinetic studies with maraviroc have shown a rapid absorption resulting at T_{max} of 30 minutes to 4 hours post dose; a modeled terminal half-life following the oral dosing of 17 hours; and pharmacokinetics are similar between males and females; between Asians, African Americans and Caucasians; and between HIV-infected patients and healthy volunteers. Multiple dose studies have shown limited accumulation on multiple dosing. Food reduces exposure with blunting of the C_{max}.

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Because maraviroc is metabolized through the CYP3A4 system we undertook an extensive drug-drug interaction program looking at the effects of co-administration with over 20 compounds or combinations. The findings from these studies

can be simplified into practical guidance for the healthcare provider.

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CYP3A4 inhibitors, such as protease inhibitors, increase maraviroc exposure 3-10-fold though no net effect is seen with the combination of tipranavir and ritonavir. CYP3A4 inducers, such as efavirenz and rifampin, decreased maraviroc exposure. Combinations of inhibitors and inducers, such as for example Kaletra plus efavirenz, led to inhibition as with the inhibitors alone. Renal substrates and inhibitors had no effect on maraviroc.

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With regard to dose selection, HIV-infected patients were selected to participate in a monotherapy study based on the presence of an R5-tropic virus identified by the Trofile assay. Exploring doses that ranged from 25 mg once daily to 300 mg twice daily, viral load reduction between 1.5 and 1.7 logs was observed in doses at or beyond 100 mg twice daily.

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Maraviroc was very well tolerated in this Phase 2a study, as well as in other Phase 1 studies, with the only event of interest being that of postural hypotension at doses at or exceeding 600 mg once daily. Based on these findings, doses of 300 mg once daily and 300 mg twice daily were selected for further study in Phase 2b/3 trials. A dose reduction of 50 percent was recommended for all CYP3A4 inhibitors to keep C_{max} no greater than the 300 mg equivalent although AUC would be greater than the 300 mg alone. This includes situations in which efavirenz was dosed with a protease inhibitor.

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The phase 2b/3 program for maraviroc includes four studies, one trial in patients naive to therapy and three in treatment-experienced. The naive study compares efavirenz to maraviroc 300 mg once daily and 300 mg twice daily, with all patients also receiving combivir.

Early last year the DSMB instructed us

that patients getting the maraviroc once daily dose should be dropped from the blinded study and offered twice daily treatment in open-label fashion. All patients are now nearing the 48-week primary endpoint and as recently as April 10th the DSMB instructed us to continue this trial. But we will not be showing data from this study this morning. We are focusing on the treatment-experienced population here today.

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The treatment-experienced program enrolled 1,265 patients. It was designed to answer a number of questions. First, to establish whether in patients with R5-tropic virus a once and/or twice daily dose would demonstrate superiority over placebo in the change in viral load at 24 weeks in the setting of optimized background therapy, in accordance with FDA guidelines on accelerated approval of antiretroviral agents.

Second, to assess the impact of administration on CCR5 inhibitor to patients with a dual- or mixed-tropic virus at baseline.

Third, to allow for collection of data in which to gauge the relative safety of maraviroc in the treatment-experienced population. As noted before, studies 1027 and 1028 are the pivotal studies in this program.

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Safety data has been collected from 1,910 patients on maraviroc and 287 patients on comparator agents across studies from all phases of the program. The safety presentation will provide a general adverse event review, as well as additional focus on a number of areas of interest including hepatic function, cardiovascular adverse events, comparator mortality rates and the incidence of infection and malignancies during the 24-week observation period. A primary focus will be on the treatment-experienced data, with particular interest in the Phase 3 studies in patients with all R5-tropic virus.

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A virology discussion will focus on two topics, first examination of clones from an already

preexisting species to studies of V3 loop alignment, and phylogenetic analyses will be presented in order to better understand the mechanism behind the switch to CXCR4 virus predominance. Second, phenotypic and genotypic analysis of clones from patients with virologic failure with R5 resistant clones will be provided to better characterize R5 viral resistance to maraviroc.

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Now I would like to introduce Dr. Howie Mayer who will review efficacy data from the treatment-experienced program.

Clinical Efficacy

DR. MAYER: Thank you, Dr. Dunne.

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I am going to briefly review the maraviroc Phase 2b/3 clinical development program; present the results of the pivotal studies in treatment-experienced patients with R5-tropic HIV-1; followed by the results of the exploratory study conducted in treatment-experienced patients

with dual/mixed-tropic HIV-1.

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First an overview of the maraviroc Phase 2b/3 clinical development program.

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Four studies are being conducted. One study in antiretroviral naive patients is ongoing. Three studies in treatment-experienced patients are being conducted, including studies 1027 and 1028 which are identical studies in treatment-experienced patients with R5-tropic HIV-1. 1027 is being conducted in North America while 1028 is being conducted in Europe, Australia and the U.S.

These are Phase 2b/3 studies evaluating two doses of maraviroc added onto optimized background therapy versus placebo added onto optimized background therapy. Randomization was 2:2:1 and the primary endpoint was change in viral load from baseline. More than 1,000 patients were randomized into the two pivotal studies, and an additional 190 patients were enrolled into a Phase

2b study in patients with dual/mixed-tropic HIV-1. Across the three studies, over 950 patients were treated with maraviroc.

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Nearly 4,000 patients had a screening tropism result in the maraviroc Phase 2b/3 clinical program. For the 3 treatment-experienced studies, 2,560 patients had a screening tropism result which was R5-tropic in 56 percent of patients, dual/mixed-tropic in 41.4 percent of patients, and X4-tropic in 2.6 percent of patients. These results are consistent with rates reported from other treatment-experienced cohorts.

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Each study has tested the 300 mg dose equivalence of maraviroc given once daily and twice daily. Given that maraviroc is a CYP3A4 substrate, the maraviroc unit dose was halved to 150 mg QD or BID in the presence of CYP3A4 inhibitors, which included all protease inhibitors except tipranavir and/or delavirdine with or without CYP3A4 inducers such as efavirenz. This dose adjustment was made

to ensure that a 300 mg equivalent C_{max} was not exceeded. For all other regimens patients received maraviroc 300 mg QD or BID.

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Now moving on to the clinical trial results from the 2 pivotal studies in treatment-experienced patients with R5-tropic HIV-1.

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This is the trial design for the 2 pivotal studies. Patients were randomized 1:2:2 to optimized background therapy plus placebo, OBT plus maraviroc QD, or OBT plus maraviroc BID. OBT consisted of 3 to 6 antiretroviral agents selected on the basis of resistance testing and treatment history. These are ongoing 48-week studies, with the primary endpoint at week 48 and a pre-planned 24-week analysis.

Patients were stratified by enfurvitide use and non-use and by viral load of less than, greater to or equal to 100,000 copies/mL at the time of randomization. Patient eligibility

criteria included R5 HIV-1 infection by the Trofile assay, a viral load of greater than or equal to 5,000 copies/mL at screening, being on a stable antiretroviral regimen or no antiretrovirals for at least 4 weeks, and resistance to 3 of the 4 drug classes, and/or at least 6 months treatment experience with at least 1 antiretroviral from 3 drug classes and at least 2 for protease inhibitors.

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The primary efficacy endpoint was the change from baseline in log transformed HIV-1 RNA, with discontinuations imputed as zero or no change from baseline. The key secondary endpoints were the percentage of subjects who achieved a viral load of less than 400 copies/mL and less than 50 copies/mL and the change from baseline in absolute CD4 cell count.

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Next will be the results of study 1027 conducted in North American.

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601 patients were randomized and 585 patients were treated. The mean age was 46. Most of the patients were white males. The median CD4 count ranged from 150-168 and the mean viral load was 4.85 log copies/mL. Approximately 40-45 percent of the patients received enfurvitide as part of OBT and about 70 percent of patients had two or fewer active drugs as part of OBT as measured by resistance testing.

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The primary efficacy results for this study demonstrated a significantly greater reduction in HIV-1 RNA for both the maraviroc QD and BID treatment groups compared to the placebo group. The mean reduction in viral load in the placebo group was approximately 1 log as compared to 1.82 and 1.95 log copies/mL in the maraviroc QD and BID groups respectively.

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A significantly greater percentage of patients who received maraviroc QD or BID achieved an undetectable HIV-1 RNA compared with the placebo

group and 60.4 percent of the patients who received maraviroc BID achieved a viral load of less than 400 copies/mL as compared with 54.7 percent of the patients who received maraviroc QD and only 31.4 percent of the patients who received placebo. Nearly half, 48.5 percent, of the patients who received maraviroc BID achieved a viral load of less than 50 copies/mL as compared to 42.2 percent of the patients who received maraviroc QD and only 24.6 percent of the patients who received placebo.

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There was also a significantly greater increase in absolute CD4 count for both maraviroc treatment groups compared to the placebo group. The increase was approximately twice as great for both maraviroc treatment groups as compared to the placebo group.

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Next will be the results of study 1028, conducted in Europe, Australia and the U.S.

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475 patients were randomized and 464

patients were treated. As in study 1027, the mean age was approximately 46 and most of the patients were white males. The median CD4 count ranged from 174-182. The mean viral load was similar to what was seen in study 1027. Approximately 40 percent of the patients received enfurvitide as part of OBT and nearly two-thirds of the patients had 2 or fewer active drugs as part of OBT as measured by resistance testing.

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As in study 1027, the primary efficacy results demonstrated a significantly greater reduction in HIV-1 RNA for both the maraviroc QD and BID treatment groups compared with the placebo group. The mean reduction in viral load was approximately 1 log greater than placebo for both the maraviroc QD and BID treatment groups. Also, in study 1027 the percentage of patients who achieved an undetectable viral load by the standard and ultrasensitive HIV-1 RNA assay was significantly greater for both maraviroc treatment groups as compared to the placebo group.

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And, as shown in 1027, there was a significantly greater increase in absolute CD4 count for both maraviroc treatment groups as compared to the placebo group.

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We have conducted combined analyses of the 1027 and 1028 data to determine any potential impact of specific co-administered antiretrovirals on the efficacy of maraviroc.

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As would be expected in this population, few patients, less than 100 overall, did not receive at least 1 protease inhibitor as part of their optimized regimen. However, approximately twice the number of patients, or more, who received maraviroc achieved a viral load of less than 50 copies/mL compared with placebo regardless of whether patients did not receive a protease inhibitor or did receive a protease inhibitor as part of their optimized background regimen.

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We also examined the impact of enfurvitide use, which was one of the two stratification factors, and approximately twice the number of patients who received maraviroc achieved a viral load of less than 50 copies/mL compared with placebo regardless of whether patients received enfurvitide or did not receive enfurvitide as part of their optimized regimen.

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We also examined the impact of adding maraviroc to an optimized regimen containing at least 1 drug known to have significant antiretroviral potency, used for the first time. For this analysis we used enfurvitide and lopinavir/ ritonavir. There was a clear additional benefit of maraviroc, with approximately 60-70 percent of patients achieving a viral load of less than 50 copies/mL.

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The same analysis demonstrated that 75-97 percent of patients receiving maraviroc in combination with enfurvitide or lopinavir/ritonavir

achieved a viral load of less than 400 copies/mL at week 24.

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We have also conducted combined subgroup analyses of the 1027 and 1028 data to determine any potential differences between the maraviroc QD and BID treatment groups not apparent from the overall primary efficacy results.

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Patients were stratified by HIV-1 RNA of less than or greater than or equal to 100,000 copies/mL. The percentage of patients who achieved an HIV-1 RNA of less than 50 copies/mL was substantially greater for both maraviroc treatment groups as compared with the placebo group regardless of low or high screening viral load. However, slightly more patients who had a screening viral load of greater than or equal to 100,000 copies/mL and received maraviroc BID achieved an undetectable viral load, 35 percent as compared to 28 percent of the patients who received maraviroc QD, and only 11 percent of the patients who

received placebo.

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Within each CD4 strata, the percentage of patients who achieved an HIV-1 RNA of less than 50 copies/mL were substantially greater for both maraviroc treatment groups as compared to the placebo group. However, within the lowest CD4 strata, less than 50 CD4 cells, nearly twice as many patients who received maraviroc BID achieved an undetectable viral load, 20 percent as compared with 11 percent of the patients who received maraviroc QD and only 3 percent of the patients who received placebo.

[Slide]

The percent of patients who achieved an HIV-1 RNA of less than 50 copies/mL was greater for both maraviroc treatment groups as compared to the placebo group regardless of the number of active drugs included as part of their optimized background regimen. However, the differences between the maraviroc groups and the placebo group were most remarkable for patients receiving two or

fewer active drugs.

[Slide]

Of patients with no active drugs available, as shown here, more patients who received maraviroc BID, 29 percent, achieved a viral load of less than 50 copies/mL compared with patients who received maraviroc QD, 18 percent, and only 3 percent of those patients who received placebo.

[Slide]

Given the anticipated overlapping plasma concentrations between maraviroc QD and BID, sparse PK sampling was conducted to estimate subject-specific exposure variables and to then determine the influence of covariates, such as OBT components on maraviroc exposure over the QD and BID dose, and to identify a potential relationship between maraviroc exposure and clinical efficacy.

[Slide]

These box and whisker plots show maraviroc average plasma concentrations by single protease inhibitors given in combination with maraviroc,

shown here. The 300 mg BID reference group from the monotherapy studies in patients is shown here, on the right. As opposed to when given with lopinavir, saquinavir or indinavir, maraviroc average plasma concentrations, when given in combination with fosamprenavir, boosted or unboosted atazanovir, fell somewhat below the plasma concentrations obtained with the 300 mg BID unboosted dose.

[Slide]

In contrast, the same plots in patients who received maraviroc 150 mg BID dose demonstrates that maraviroc average plasma concentrations were at least at the level of an unboosted 300 mg BID dose for all co-administered protease inhibitors.

[Slide]

These plots show maraviroc average plasma concentrations in patients who received maraviroc 300 mg QD and BID dose with either tipranavir, ritonavir or a non-protease inhibitor-containing regimen. As expected, only the 300 mg BID dose achieved exposure similar to the 300 mg BID

reference regimen taken from the monotherapy studies in patients. In addition, exposures were similar for both tipranavir, ritonavir and non-protease inhibitor containing-regimens.

[Slide]

We conducted an exposure-response efficacy analysis looking at both virologic and immunologic endpoints such as an HIV-1 RNA less than 50 and less than 400 copies/mL and CD4 change from baseline. The method was generalized additive modeling and considered prognostic factors including dose and exposure, baseline laboratory characteristics, co-administered agents and demographics.

[Slide]

The results demonstrate a relationship between maraviroc exposure and response with the likelihood of failure, defined here as a viral load of greater than 50 copies/mL at week 24 increasing with decreasing concentrations. The probability of success approaches a maximum at approximately 50 ng/mL for C_{min}, on the left, and at approximately

100 ng/mL for C-average, on the right.

[Slide]

We have also conducted a number of analyses evaluating the impact of tropism changes occurring during the clinical program.

[Slide]

The potential clinical impact of changes in tropism in the clinical program was assessed by evaluation of changes in CD4 count in patients failing with a CXCR4-using virus compared to those failing with an exclusively CCR5-using virus. Overall, treatment failure was much less common for both maraviroc treatment groups than for the placebo group.

In addition, patients who failed on maraviroc had greater increases in CD4 count, increases of 49 and 71 cells in the maraviroc QD and BID groups respectively compared to an increase of only 14 cells in the placebo group. Similar differences were also observed in patients who were R5-tropic at baseline and R5-tropic at the time of failure. Nearly twice the number of patients,

which represented approximately 7.6 percent of all maraviroc treated patients who failed on maraviroc, had a CXCR4-using virus versus an exclusively CCR5-using virus.

However, even those patients who failed on maraviroc with a dual/mixed or X4 virus had increases in CD4 count that were greater than that seen in the overall placebo population that failed. Lastly, 7.6 percent of the patients had a change in tropism result between screening and baseline, and those patients who failed on maraviroc also had increases in CD4 count that were at least as great as those seen in the placebo patients who had a change in tropism between screening and baseline and who failed. These last results are similar to what was seen in study 1029, which I will be discussing later on during this presentation, where we specifically investigated the use of maraviroc in a dual/mixed-tropic population.

[Slide]

In the 7.6 percent of patients who had a tropism change between screening and baseline, some

of these patients achieved a viral load of less than 50 copies/mL on maraviroc treatment at a rate that was similar to or greater than that seen in the placebo group. The absence of any evidence of a negative effect on virological outcome compared with placebo in these patients is also consistent with what was seen in study 1029, conducted in patients with non-CCR5-tropic virus.

[Slide]

A total of 47 patients, 44 in the maraviroc treatment groups with CCR5-tropic virus at baseline and who failed with CXCR4 or dual/mixed-tropic virus had at least one follow-up visit. More than two-thirds of the maraviroc-treated patients, 30 of 44, had reverted back to an R5 tropism result by the last follow-up visit. For the 14 patients whose virus remained dual/mixed or CXCR4-tropic the median time of follow-up was only 16 days. In contrast, for those patients whose virus reverted back to a CCR5 tropism result the median time to follow-up was approximately 203 days. This suggests that

CXCR4-using virus, emerging in the setting of maraviroc treatment, will revert back to a CCR5-using virus in the absence of selective suppression of R5-tropic virus by maraviroc.

[Slide]

I will conclude with the results of study 1029, an exploratory study conducted in treatment-experienced patients with dual/mixed-tropic HIV-1. The study design and primary and secondary endpoints were similar to the 1027 and 1028 studies, and 190 patients were randomized and 186 patients were treated. The mean age was approximately 44. Most of the patients were white males. The median CD4 count was substantially lower than in the R5 population, approximately 40. The mean viral load was in excess of 5 log copies/mL for all treatment groups. More than half of the patients received enfurvitide as part of their optimized therapy, and 167 patients had dual/mixed-tropic virus at screening and represented the primary efficacy population.

[Slide]

The primary efficacy results for this study demonstrated no significantly greater reduction in HIV-1 RNA for either the maraviroc QD or BID treatment groups as compared to the placebo group. However, there was no evidence of a negative effect on virologic outcome.

[Slide]

Similarly, there was no significant difference in the percentage of patients who achieved an undetectable HIV-1 RNA compared with the placebo group for both the less than 400 and less than 50 copies/mL analysis. However, slightly more patients achieved a viral load of less than 400 copies/mL and less than 50 copies/mL in the maraviroc BID treatment groups as compared to the other two treatment groups.

[Slide]

For the dual/mixed-tropic population the mean change from baseline to week 24 in CD4 count was greater for both the maraviroc QD and BID treatment groups by 24 and 26 cells respectively as

compared with the placebo group. For those patients who failed, the mean change in CD4 count from baseline was also greater for patients who failed on maraviroc versus patients who failed on placebo. In those patients who failed with CXCR4-using virus only, which was much more likely to occur on maraviroc due to selective suppression of the R5 virus population, increases in CD4 count were also seen that were similar to the overall maraviroc population that failed and, therefore, greater than the overall placebo population that failed.

[Slide]

So, in summary, in treatment-experienced patients with R5-tropic HIV-1 and few remaining treatment options, maraviroc added to optimized background therapy demonstrated significantly greater virologic suppression and CD4 cell increases compared with placebo added on to optimized background therapy in two independent studies.

There are subgroups of patients where

there appears to be an efficacy difference favoring the maraviroc BID dose, including those patients with high viral loads, patients with very low CD4 counts and no other active antiretrovirals available.

[Slide]

Patients with R5-tropic HIV-1 failing on maraviroc had mean increases in CD4 count that were greater than placebo even when failing in the context of a change in tropism to a CXCR4-using virus.

Of patients with R5-tropic virus at baseline who failed on maraviroc plus OBT, nearly twice as many patients had a change in tropism to dual/mixed- or X4-tropic as compared with remaining R5-tropic. However, the virus in most patients who failed on maraviroc with dual/mixed-tropic or X4-tropic virus reverted back to R5-tropic during the follow-up period and this was directly correlated with the length of observation.

[Slide]

Lastly, in treatment-experienced patients

with dual/mixed-tropic HIV-1 maraviroc plus OBT did not lead to a significantly greater reduction in HIV-1 RNA, but was also not associated with an adverse virologic outcome and demonstrated greater CD4 increases as compared with placebo plus OBT. These results were also observed in those patients in studies 1027 and 1028 who had a change in tropism from R5 to dual/mixed between screening and baseline.

[Slide]

With that, I would like to turn it over to Dr. Steve Felstead who will summarize the safety results.

Safety and Toleration

MR. FELSTEAD: Thank you, Dr. Mayer. Good morning.

[Slide]

I would like now to turn to maraviroc safety and toleration evaluation.

[Slide]

This slide shows an outline of my presentation. I will first cover the findings in

short-term trials of maraviroc in healthy volunteers and asymptomatic HIV-1-infected subjects. Then I will turn to the data from the Phase 2b/3 program, presenting a brief general overview before focusing on cardiovascular, hepatic and immune function safety, closing with a summary of the mortality rate observed.

[Slide]

Nearly 700 subjects participated in short-term trials with dose duration extending from 1-28 days. The goals of the program were to establish the maximum tolerated dose, the dose-limiting adverse effects, drug-drug interactions and the dose-response relationship to viral load reduction previously summarized by Dr. Dunne.

[Slide]

Postural hypotension was found to be the dose-limiting adverse effect with maraviroc. The frequency of postural hypotension observed in subjects receiving 300 mg was not different from placebo. The frequency increased compared to

placebo at doses of 600 mg and above and 1,200 mg was the maximum tolerable dose. Postural hypotension was generally observed within 1-4 hours, around the time of C_{max}. A non-invasive cardiac function study showed no adverse effect on supine cardiac index at 900 mg, consistent with a mild vasodilator. The mechanism remains uncertain.

[Slide]

Preclinical in vitro evaluation showed maraviroc able to inhibit binding of 15 percent to the hog [ph] receptor at concentrations of 3 micromolar, 10 times the projected C_{max}. QT prolongation was observed in dogs and monkeys at 6- and 12-fold the C_{max} of the proposed therapeutic dose respectively, but no arrhythmias were observed with high concentrations in either species.

[Slide]

Therefore, a thorough QTc study was designed to assess the effects of maraviroc on QTc interval in healthy volunteers with a positive control. This was a randomized, placebo-controlled, crossover study in which 61

healthy subjects received single doses of maraviroc 100 mg through 900 mg with moxifloxacin 400 mg, and individual correction for heart rate was derived. The mean difference in QTc interval compared to placebo was less than 4 misec for maraviroc at any dose. The 90 percent upper limits of the confidence interval of the QTcI prolongation was less than 7 misec. Moxifloxacin demonstrated a 12-14 misec change. A concentration effect relationship was established using PK/PRODUCT modeling, projecting a change of 1 misec for every 1,000 ng/mL increase. The maximum concentration observed was 2,360 ng/mL in this study. The maximum concentration observed in the Phase 2b/3 studies was 2,470 ng/mL. I will discuss QTc measurements in Phase 3 shortly.

[Slide]

Our conclusions from our Phase 1/2a program were that maraviroc was well tolerated at unit doses of up to 300 mg. Postural hypotension was identified as the dose-limiting toxicity with a frequency greater than placebo at maraviroc unit

doses of 600 mg and above and maraviroc caused no clinically relevant effect on QTc.

[Slide]

I would now like to turn to the safety and toleration data from Phase 2b/3.

[Slide]

A total of 1,212 patients have received maraviroc in Phase 2b and 3 trials. The treatment-experienced patients comprised 840 patients who received maraviroc in Phase 3 studies in patients with R5-tropic virus. A further 124 patients infected with non-R5-tropic virus plus a total of 964 patients received double-blind maraviroc in treatment-experienced studies.

I will focus on the Phase 3 studies in patients infected with R5-tropic virus. Except when unwanted pharmacology is being considered, or the events are rare, or patient numbers are small when all three treatment experience studies are combined, and the titles of the slides I will show indicate which studies are included, the open-label data and the treatment-naive QD data are considered

only for individual events.

[Slide]

The safety data is drawn from systematic follow-up of all patients through to a minimum of 24 weeks and a maximum of 48 weeks. As is common in studies of this design, patient follow-up is much reduced on placebo because of dropouts due to lack of efficacy. Therefore, median duration of dosing of maraviroc is just under 8 months compared with 5 months on placebo. Therefore, patient-years exposure is over 2.5 times greater on each maraviroc treatment group compared with placebo.

[Slide]

The Kaplan-Meier plot of discontinuations shows that the placebo patients begin to discontinue between weeks 8 and 12, and the curves continue to slowly separate below this. At the time of the NDA, approximately 4 times as many patients had been followed for over 300 days on maraviroc compared to placebo.

[Slide]

This is an overview of the safety findings

from the two Phase 3 studies in patients infected with R5-tropic HIV-1. Adverse events are reported slightly more frequently in the maraviroc treatment groups, at 88-90 percent, compared to the placebo patients, at 83.7 percent. However, patients discontinuing due to adverse events were low in number and less than 5 percent in any treatment group, with no differences noted between maraviroc twice daily and placebo. Furthermore, the proportions of patients reporting serious adverse events are evenly balanced across treatment groups. Category C adverse events occurred in a similar percentage of patients in the placebo and maraviroc QD treatment groups and slightly less in the maraviroc BID group. Twelve deaths were reported in double-blind drug over the 28 days of discontinuation of drug, 11 on maraviroc.

[Slide]

This slide gives a similar presentation for the Phase 2b study in patients infected with non-R5-tropic virus. Exposure in this study is evenly balanced between the treatment groups, 25 to

28 patient-years. Excepting slightly more category C adverse events being reported in the maraviroc QD group, there are no notable differences seen with respect to frequency of adverse events, discontinuation due to adverse events or serious adverse events. Five deaths were reported, 3 in the maraviroc treatment group.

[Slide]

I will now show the most frequently reported all-causality adverse events occurring at greater than 10 percent incidence in any treatment group in the Phase 3 studies.

[Slide]

Only cough and upper respiratory tract infection are reported more frequently on maraviroc at either dose compared to placebo. I will discuss this in more detail shortly. Other adverse events are typical of the patient population and reported in similar frequency to placebo despite longer duration of follow-up on maraviroc.

[Slide]

I will now turn to the cardiovascular

safety evaluation of maraviroc.

[Slide]

Postural hypotension was specifically evaluated at clinic visits at baseline, week 2 and week 24. As postural hypotension was systematically evaluated I have merged the three treatment experience studies. As can be seen, there is a slight imbalance at baseline with a lower proportion observed with postural hypotension in the placebo group compared with the maraviroc treatment groups, here. By week 2 the event rate had increased in all treatment groups and then was reduced slightly at week 24.

To assess for bias we also examined postural hypotension at unplanned for-cause assessments and at early termination. Overall, postural hypotension is observed a little more frequently in the maraviroc groups compared to the placebo group.

[Slide]

ECG measurements were also conducted in all Phase 2b/3 trials at baseline and week 24.

Again, I have merged the data across the 3 treatment-experience studies. The baseline mean QTc was around 400 misec in all 3 treatment groups. The change from baseline was assessed in approximately 45 percent of patients and the mean increase was less than 3 misec in all treatment groups, down here.

[Slide]

Turning to the reported ischemic adverse events in the treatment-experienced program, with the exception of 3 patients, 1.4 percent in the placebo group, all other events were reported on maraviroc therapy. These are transient ischemic attacks. Focusing on myocardial infarction, 3, 0.6 percent, of definite or possible myocardial infarctions were reported on maraviroc QD therapy. The only ischemic event reported on maraviroc BID was a myocardial infarction.

Although there is an imbalance compared to placebo, the specific myocardial infarction event rates were within the range reported from patients with similar prior duration of HAART. As expected,

all these patients had a range of cardiovascular risk factors.

[Slide]

In conclusion on cardiovascular safety, maraviroc is associated with only a slight excess of measured postural hypotension compared to placebo, supporting the dose adjustment strategy. Maraviroc is not associated with QTcF prolongation and, although more ischemic events are observed on maraviroc than placebo, the event rate is consistent with what is expected for this heavily pretreated population.

[Slide]

Moving on to laboratory testing and hepatic safety, a battery of routine laboratory tests were performed at baseline and at each clinic visit. No notable differences in frequency of abnormalities were seen between maraviroc treatment groups and placebo. However, in 2005 GlaxoSmithKline discontinued another CCR5 antagonist, aplaviroc, because of drug-related hepatotoxicity. Further, in December, 2005 at the

HIV entry meeting Dr. Mayer reported a case of severe liver dysfunction, requiring transplantation, in a maraviroc patient from a treatment-naive program. Although the cause of this liver dysfunction in this patient was accepted to be perhaps more likely due to izoniazide toxicity, izoniazide being introduced at the time of screen for the study, a role of maraviroc could not be excluded. Therefore, I am going to focus the presentation on liver function test data derived from the Phase 3 clinical trials in treatment-experienced patients.

[Slide]

In the Phase 3 trials in patients infected with R5-tropic virus, 1 percent of the study population discontinued with hepatic-related adverse events across the 3 treatment groups. Grade 3 AST elevations were seen in approximately 3 percent of patients in the 3 treatment groups, and grade 4 AST abnormalities were seen in 0.7 and 1.4 percent of maraviroc QD and BID groups respectively, as shown here. ALT is usually

considered the most sensitive marker of hepatocellular disruption. A lower percentage of patients experienced grade 3 ALT abnormalities in the maraviroc BID treatment group, and grade 3 abnormalities were seen in 1 percent or less of the patients in the 3 groups. The total bilirubin abnormalities were usually due to concomitant atazanovir.

[Slide]

This table presents the liver function test data from the Phase 2b study in treatment-experienced patients infected with non-R5-tropic virus. No differences from placebo were noted for any of the 3 parameters.

[Slide]

I would now like to examine specific subgroups for safety evaluation of hepatic function, tipranavir and/or atazanovir concomitant use in patients infected with hepatitis C or B.

[Slide]

Overall, nearly 150 patients received tipranavir, evenly split across the 3 treatment

groups, 1:2:2. No evidence of an adverse trend was observed with maraviroc-tipranavir co-administration in ALT abnormalities. Most of the total bilirubin abnormalities were attributed to atazanovir. Just over 180 patients received atazanovir in the Phase 3 studies. Maraviroc QD with atazanovir appeared to show a greater frequency of total bilirubin elevations, but this was not noted in the maraviroc BID group compared with maraviroc-placebo group.

[Slide]

A few patients were co-infected with hepatitis C, as defined by measurable RNA, just 4.2 to 7.4 percent across the groups. To maximize the database I have included all 3 treatment-experience studies. Six co-infected subjects were observed to have grade 3 or 4 ALT abnormalities, 1 in the placebo group, 3 in the maraviroc QD group and 2 in the maraviroc BID group. Similarly small numbers were found to have hepatitis B, as defined by being surface antigen positive. Three grade 3/4 abnormalities were observed in placebo and the

maraviroc treatment groups.

[Slide]

So, to conclude, in the treatment-experience studies maraviroc has no association with liver function test abnormalities. Adding maraviroc to tipranavir or atazanovir does not increase the frequency of observed liver function test abnormalities. Maraviroc is not associated with an increase in abnormal LFTs in co-infected patients, but the number assessed is too small to draw conclusions.

[Slide]

Turning now to the evaluation of infections and malignancies in the maraviroc program.

[Slide]

This slide summarizes the percentage of patients reporting category C events in the 2 pivotal studies. The percentage of patients diagnosed with category C infections is lowest overall in the maraviroc BID arm, at 4.2 percent. With the exception of herpes simplex in the

maraviroc QD group, at 2.4 percent, and esophageal candidiasis in the same group, 2.9 percent, individual category C infections are reported in less than 2 percent of patients, and scattered across all 3 treatment groups.

[Slide]

This is a busy slide so I will take a little time to walk you through. It summarizes more frequently reported infections of interest from the Phase 3 studies in the R5 treatment-experienced patients, and includes herpes simplex virus infections and candidal infections regardless of their designation as category C infections. I should note that we have merged event terms here so this may be a maximal estimate.

The left column presents the percentage of subjects reporting infections with exposure adjustment in the column to the right. So, that is percentage of patients and that is the exposure adjustment as we go across the treatment groups. HSV infections appear more frequently in the maraviroc BID group even after exposure adjustment,

as shown there. Candidiasis, however, is seen less frequently in the maraviroc BID group compared to placebo after exposure adjustment, 6.5 compared to 12.2. Upper respiratory tract infections, laryngitis and influenza and perhaps bronchitis are more frequently observed in the maraviroc treatment groups compared to placebo even after exposure adjustment. However, pneumonia is reported twice as frequently in the placebo group compared to maraviroc, here 11.2 versus 3.5 or 5.1.

I should note that these diagnoses are not necessarily microbiologically or serologically confirmed. I should also note that simple exposure adjustment may not be adequate for seasonal infections. However, to reiterate the overall evaluation, infection rates in patients receiving maraviroc compared to placebo overall are very similar, 118 events per 100 patient-years, 120.7 per 100 patient-years and 126 per 100 patient-years.

[Slide]

Turning to malignancies, following the

reporting of all lymphomas in 90 patients treated in the ACTG study 5211, particular attention was paid to malignancy and lymphoma in the maraviroc program. At the time of filing the NDA, 5 biopsy-confirmed lymphomas had been reported on double-blind therapy in the 1,049 CCR5-tropic patient population, 2 of these in the placebo group. A further biopsy-confirmed lymphoma was reported in a patient receiving open-label maraviroc following placebo double-blind therapy. In addition, 1 suspected CNS lymphoma was reported in the maraviroc BID group. Overall, no evidence was found for maraviroc being associated with an excess of lymphoma compared to placebo. No lymphomas have been reported in the non-R5 study at the time of the NDA. Kaposi's sarcoma was reported slightly more frequently in the placebo group.

[Slide]

Other malignancies were also so assessed and are summarized in this slide. No evidence was found for a relationship to maraviroc. Only anal cancer was reported by more than one patient per

treatment group and is less frequently observed on maraviroc despite longer duration of follow-up.

[Slide]

So, in conclusion, the data obtained so far suggest that maraviroc is not associated with an excess of category C infections or malignancies, including lymphoma, compared to placebo. Maraviroc doesn't appear to be associated with other malignancies. Maraviroc may be associated with an excess of upper respiratory tract infections and herpes simplex virus infections.

[Slide]

I will now review the mortality rates observed in the treatment-experience program.

[Slide]

The top part of this slide shows all the deaths reported in the 3 treatment-experience studies, including patients no longer receiving double-blind therapy. The lower part of the table shows standardized reporting of deaths on double-blind therapy or within 28 days of follow-up.

Study 1028, conducted in Europe, the U.S. and Australia, shows an imbalance, with no deaths reported in the placebo group. However, overall the percentages of deaths are similar between treatment groups. The deaths observed were due to a variety of causes characteristic for this population.

[Slide]

This slide converts the incidence, as shown in the lower part of the slide, into mortality rates per 100 patient-years of study drug exposure. Mortality rates are similar across treatment groups, being between 2 to 2.8 per 100 patient-years. Methodology may vary but these rates appear broadly similar to those observed with other recently approved drugs.

[Slide]

So, to conclude, mortality rates are similar to historical data. The causes of death are as expected for the population studied, with no single reason observed. There is no evidence for a contribution of maraviroc to mortality in these

clinical trials.

[Slide]

So, to summarize, maraviroc BID is as well tolerated as maraviroc QD. Adverse events on maraviroc are similar in frequency and nature to placebo. Maraviroc is associated with a slight excess of measured postural hypotension at the recommended doses. Maraviroc is not associated with QTc prolongation. Ischemic adverse events are seen more frequently in the maraviroc treatment arms but the event rates appear consistent with expected event rates from a heavily pretreated population.

[Slide]

Maraviroc is not associated with elevations on hepatic enzymes in treatment-experience studies so far. And, maraviroc is not associated with an excess of category C events. Maraviroc may be associated with an excess of upper respiratory tract infections and HSV infections. Maraviroc is not associated with excess in mortality compared to

placebo.

[Slide]

With that, I would now like to hand over to Dr. Mike Westby who will cover the virology.

In Vitro and In Vivo Tropism and Resistance Evaluation

DR. WESTBY: Thank you, Dr. Felstead. Good morning, everyone.

[Slide]

I would like to start this morning by recapping that there are many reasons why viral escape to maraviroc will be different from anything seen previously. First of all, maraviroc binds to a host protein. All licensed antiretrovirals target HIV proteins. Secondly, maraviroc is only active against CCR5-tropic strains and, finally, maraviroc is not a competitive inhibitor. CCR5 antagonists, including maraviroc, are allosteric inhibitors. In other words, they don't directly block the interaction between CCR5 and gp120. Given these unique properties, there are two virologic issues relevant to the proposed

indication.

[Slide]

In the patients in whom CXCR4-using virus is detected, does virus emerge by mutation of a CCR5-tropic virus whilst on treatment, so-called co-receptor switching? Or, is it, rather, detection on treatment of a preexisting CXCR4-using population? For patients who fail with a CCR5-tropic virus, we wanted to look for evidence and incidence of maraviroc resistance and then determine the phenotypic and genotypic markers of that resistance.

[Slide]

Firstly I would like to address changes in viral tropism occurring on the maraviroc program.

[Slide]

In order to provide data in time for this submission an exploratory and detailed viral investigation was conducted in a blinded fashion on pretreatment and on-treatment samples from 20 patients in whom CXCR4-using viruses were detected on treatment. The selection of patients for this

study is shown on the next slide.

[Slide]

All patients who began blinded therapy in either 1027 or 1028 by June 1st, 2005 were followed for 24 weeks. This strategy was followed to complete the analysis in time for the submission and ensured that the patient population was representative of the total population enrolled in the Phase 3 studies. By December, 2005 patients were characterized, as shown, based on their outcome. I should note that more than half of the patients were censored from the analysis as at week 24 they had no detectable virus. Fifty patients were identified as having CXCR4-using virus on treatment; 15 remained on study drug at week 24 and 35 have been discontinued due to lack of efficacy. Twenty of these patients, 14 failures and 6 responders, were selected for detailed clonal analysis.

[Slide]

The reason for studying a subgroup of patients in great detail was to be able to have

sufficient sensitivity to identify viruses present at a low frequency in the pretreatment sample. A simple probability model determined how many clones per sample were needed to be screened for tropism in order to identify with 99 percent probability the CXCR4-using population present at a 5 percent frequency. Therefore, viral tropism and gp120 sequencing was performed on 192 envelope clones randomly selected from the baseline sample. These were compared to 48 envelope clones taken from an on-treatment sample. V3 alignments and phylogenetic trees were constructed to try and understand the origin of the on-treatment CXCR4-using virus.

[Slide]

The summary of the findings is shown here. No evidence was found to suggest that CXCR4-using virus is selected by mutation and co-receptor switching of CCR5-tropic viruses while on treatment. Rather, CXCR4-using clones were either detected at a low frequency in the baseline sample or the on-treatment CXCR4-using clones were so

genetically distinct from the pretreatment CCR5 clones that their origin from a preexisting CXCR4-using virus was by far the most likely explanation. There appeared to be no mechanistic differences in virus origin between the patients on placebo, and we now know there were 4 in the 20, and those on maraviroc, 16. And, changes in viral tropism were seen in the absence of treatment failure although, as I said earlier, for most patients who are successes we are not able to investigate tropism at 24 weeks because they didn't have sufficient virus.

On the following slides I will show two data sets which illustrate the main points.

[Slide]

Shown on this slide is a patient graph of response over time. The change in viral load is shown in yellow and the change in CD4 is shown in blue. The patient received maraviroc from day 1, which is the white dashed line; failed therapy at week 8, as shown by the green dashed line; and stopped treatment here, as shown by the red line.

The viral tropism as measured by the Trofile assay in the clinical program is shown along the top. You can see that the patient's virus is CCR5-tropic at entry; becomes dual/mixed-tropic on treatment; and following cessation of therapy reverts to be CCR5-tropic.

[Slide]

Shown on this slide are the results of the clonal tropism testing of 192 clones at baseline, on the left, and 48 clones on treatment, on the right. Each square represents a single clone and the colors indicate the viral tropism. Red indicates an R5-tropic clone; blue, a dual-tropic clone; green, an X4-tropic clone. A white square indicates a non-functional clone in the assay.

The results on this patient identify CXCR4-using clones present at approximately 7 percent in the baseline sample. By week 4, however, only CXCR4-using clones were identified in the sample. The sequences representative of pretreatment and post-treatment clones were then compared and this is shown on the next slide.

[Slide]

The week 4 and baseline CXCR4-using clones are shown in white and the CCR5 clones are shown in yellow. The week 4 and baseline CXCR4-using clones are highly related in sequence with 8 or more amino acid differences from the R5-tropic clones. Thus, the conclusion is that the CXCR4-using clones preexisted the maraviroc treatment phase.

[Slide]

This is the second patient I would like to show you. As with the previous example, this patient's virus was R5-tropic at baseline; became dual-tropic on therapy; and reverted to CCR5-tropic after maraviroc treatment was stopped.

[Slide]

In contrast to the last patient, no CXCR4-using clones were detected in the baseline sample. All squares are either white or red. By week 4 only CXCR4-using clones were detected.

[Slide]

Neighbor-joining and maximum phylogenetic trees were drawn based on nucleotide sequences from

all 250 clones from the patient, spanning a region of approximately 290 nucleotides. All CXCR4-using sequences on treatment were genetically distinct from the baseline R5-tropic clones. Baseline R5 clones are shown here at week 5, CXCR4-using clones are shown there. This is further illustrated by the representative V3 loop sequences shown below. The R5 sequence is shown here, the week 4 dual-tropic sequence is shown here. Therefore, as with the last patient, the conclusion is that the on-treatment CXCR4-using clones originated from a CXCR4-using population that preexisted the maraviroc treatment phase.

[Slide]

For the remainder of the presentation I will concentrate on maraviroc resistance with continued CCR5 usage. As mentioned at the beginning of my presentation, CCR5 antagonists are allosteric inhibitors of virus entry.

[Slide]

The impact of this mechanism of action on the selection of virus resistance to maraviroc is

schematically shown on this slide. Sensitive virus, shown on the left, only recognizes the free-form of the receptor. When maraviroc is bound the virus it is no longer able to recognize the receptor and entry is inhibited. Resistant viruses, however, recognize CCR5 differently, such that they can now recognize free or bound receptors, shown here on the right. The consequence of this in drug susceptibility assays is that dose-response curves which do not reach 100 percent inhibition are obtained. This is shown on the next slide.

[Slide]

Maraviroc resistant virus was selected by serial passage of the CC1/85 strain through peripheral blood lymphocytes. Although the starting culture and drug-free passage control can be fully inhibited, as shown by the yellow and red dose-response curves, the resistant, shown in blue, remains CCR5-tropic but cannot be fully inhibited even at the highest drug concentration. It is worth noting that the IC_{50} in this virus is not

changed and this is why it is not a reliable marker of maraviroc resistance.

[Slide]

Maraviroc resistant viruses generated in vitro also have rare mutations in the gp120 V3 loop. As shown on this slide, 2 different virus strains had different amino acid substitutions and deletions. The resistant variant of CCR5, shown on the left, has 2 mutations at positions 19 and 26 with a partial mutation shown here, while the resistant RU570 virus has a 3 amino acid mutation at the crown of the V3 loop. Site-directed mutagenesis of the allonene to isolucene to valine mutations in CC1/85 confirm their importance in conferring the resistant phenotype.

[Slide]

Based on these in vitro findings, the incidence of maraviroc resistance was investigated in vivo by studying all 38 patients who failed blinded treatment in the 267 patient cohort described earlier.

[Slide]

Paired pretreatment and failure samples were tested for phenotypic susceptibility to maraviroc. The study was conducted in a blinded fashion with pre-agreed criteria for resistance. Dose-response curves that didn't reach 95 percent inhibition at the maximum concentration tested were deemed to have resistance to maraviroc. This cutoff in maximum percent inhibition, or MPI, was based on preclinical findings and is shown by the blue dashed line in the following slides. We can now see that 25 of the patients who failed actually received placebo and 13 patients received maraviroc once daily or twice daily.

[Slide]

On this slide are shown the results and the baseline samples. As shown, none of the baseline samples from either the placebo or maraviroc patients were resistant to maraviroc in that they all fell on or above this line.

[Slide]

In contrast, 4 patients, all of whom we know now received maraviroc, had virus which was

resistant to maraviroc at failure. Although not shown on this slide, virus from one of the placebo patients did become resistant, as evidenced by maximum percent inhibition of less than 95 percent, but only after receiving maraviroc as open-label.

[Slide]

As with the preclinical studies of resistance, mutations in the gp120 V3 loop appeared to play a key role in conferring the resistant phenotype. Site-directed mutagenesis was performed on the V3 loops of envelope clones from baseline and failure for the 4 patients I showed on the previous slide. For each patient we have a baseline sequence, shown in the top; the mutations which were associated with failure, as shown here in a representative failure clone and the mutations were either knocked in to the start sequence, shown here, or knocked out of the failure sequence, shown there. The susceptibility to maraviroc is shown here.

For patient 8 and 14 mutating the residues, highlighted in yellow, into the start

sequence or out of the failure sequence conferred resistance or sensitivity respectively, indicating these mutations were both necessary and sufficient to confer resistance. So, for this top patient introducing these residues whose resistance these residues take when they were taken out leads to sensitivity.

For patient 4, knocking the mutations out of the failure clone did restore sensitivity, indicating that they were necessary for maraviroc resistance, while knocking them into the start sequence was not sufficient to confer resistance alone. In the case of patient 1, mutation with the asparagine residue in the start sequence was sufficient to confer resistance, shown here. Knocking this mutation out of the failure clone did increase sensitivity to maraviroc, although there was still reduced maximum percent inhibition of 91 percent.

[Slide]

In summary, the preclinical and clinical data is consistent with maraviroc's non-competitive

mechanism of action. Dose-response curves with plateaus in maximum percent inhibition are a phenotypic marker of maraviroc resistance and mutations in the gp120 V3 loop appear to play a key role.

[Slide]

As shown by Dr. Mayer earlier, CXCR4-using virus was detected in approximately two-thirds of patients who failed therapy with maraviroc. An intensive clonal analysis supports the detection on treatment of CXCR4-using virus as being a consequence of selective suppression of CCR5-tropic clones by maraviroc, thus, reducing the relative proportion in the plasma. This explanation is further supported by the reversion to R5 tropism in most patients during subsequent off-drug follow-up.

[Slide]

In patients failing with CCR5-tropic virus, maraviroc resistance was detected in approximately 30 percent of the patients. gp120 sequencing and site-directed mutagenesis has highlighted multiple pathways to maraviroc

resistance. The correlation between markers of maraviroc resistance and clinical outcome is ongoing but collectively the virology studies support maraviroc acting as a highly selective and potent inhibitor of CCR5-tropic viruses.

[Slide]

I would now like to hand over to Dr. Kuritzkes, whose slides I seem to have lost.

[Laughter]

Medical Need and Place in HIV Armamentarium

DR. KURITZKES: Thank you very much, Dr. Westby. I appreciate the opportunity to address the committee this morning.

[Slide]

I would like to speak briefly on the role of maraviroc and antiretroviral therapy for treatment-experienced patients and the need and potential clinical utility of CCR5 antagonists.

[Slide]

As Dr. Laessig mentioned in her introduction to this morning's session, despite the availability of a large number of drugs for the

treatment of HIV infection, the accumulation of drug resistance over time remains a problem, as indicated by these data from the SHEET cohort in London, recently published by Andrew Philips, showing that as treatment failure accumulates, so does the prevalence of drug resistance, mutations and viruses from those patients.

[Slide]

Earlier data from Doug Richman and Sam Bazetti, developed from the HICKS cohort, demonstrated the high prevalence of drug resistance in patients who were viremic and had received treatment or were receiving treatment, indicating an overall prevalence of approximately 75 percent, and particularly 50 percent prevalence of dual class and 13 percent prevalence triple class drug resistance. It is really from many of the patients who were in care at the time that these data were accumulated who continue to be the patients in whom we struggle to find regimens that are going to be successful today.

[Slide]

Looking at some more recent data, at the retrovirus meeting two years ago the Centers for Disease Control estimated that a little bit more than a quarter of a million patients in the United States were receiving antiretroviral therapy today, and at last year's drug resistance meeting Joe Eron and colleagues presented data suggesting that approximately 10 percent of their patient population in Chapel Hill who were viremic had evidence of triple class resistance, and these data were recently published by Nepravnik and colleagues. I think if you look at clinics across the country, one comes up with a figure of somewhere between 10 and 15 percent of patients who are in care, on therapy, who would be classified as having triple class resistance. If you do the math, that estimates then that there are somewhere between 25,000 and 40,000 patients who could benefit from better options for treating drug resistant HIV infection.

[Slide]

Now, the goals of therapy in this group of

patients have shifted dramatically over the last several years. Just four years ago one would have said that the goals of treatment in highly antiretroviral-experienced patients would be, first and foremost, to preserve immune function, to do so by maximizing the reduction in plasma HIV RNA but without the expectation that in most patients full suppression would be achievable, and to do so in a way that minimized the toxicity.

More recently, in the updated guidelines for treatment of HIV-infected patients from the Department of Health and Human Services, as well as the guidelines from the International AIDS Society USA panel, both published in the last six to nine months, it has been recognized that with the advent of new and more potent agents, including novel protease inhibitors and drugs in newer classes, full viral suppression is once again achievable and is now the appropriate goal of salvage therapy in highly treatment-experienced patients. But this goal requires the use and availability of multiple active drugs in order to achieve full suppression

and, of course, we wish to continue doing so in a way that minimizes toxicity for the patient.

[Slide]

So, why are CCR5 antagonists needed? First of all, many highly treatment-experienced patients have extensive resistance to drugs in existing classes, including at least partial resistance to even the newer protease inhibitors. Second, clinical trial experience shows that no single new drug is likely to have durable activity without the use of additional active agents. Third, the use of several new and active drugs is going to be necessary in order to achieve and maintain full viral suppression over the long term.

[Slide]

This point is illustrated in this slide in which I have aggregated data from several of the most recent pivotal trials of drugs that have been approved for highly treatment-experienced patients over the last several years. These data are pulled from the 24-week results of the intention-to-treat analyses from either published or presented data

from the most recently approved drugs, including enfurvitide, tipranavir and derunavir and for the two maraviroc studies shown separately.

The graph on the left shows the proportion achieving a 1-log reduction. The graph on the right shows the proportion achieving less than 50 copies/mL. The blue bars are the results for patients receiving the study drug and the red bars are for the patients in the placebo or control groups in the respective studies.

You can see that over time the proportion achieving a 1-log reduction has increased dramatically, as has the proportion achieving less than 50 copies. But when we look at the less than 50 copy result, still only about half of the patients are achieving that when only one of the new drugs is used and, therefore, we need to be able to combine these with other newer drugs.

[Slide]

What are the potential benefits of maraviroc? Well, as you have seen from the presentation from the clinical trials data, the

drug is a potent inhibitor of R5 HIV in highly treatment-experienced patients when combined with an optimized background regimen. The drug is safe and well tolerated in studies to date. And, importantly, there has been no demonstrated adverse consequence of administration to patients in whom dual/mixed or X4 virus emerges or was inadvertently present at the time of drug initiation.

[Slide]

So, how should maraviroc be used? Well, in my view, maraviroc should be used in combination with other active drugs in antiretroviral treatment-experienced who are infected with R5 virus.

I would like to turn this back over to Dr. Dunne.

Conclusions

DR. DUNNE: We presented data today that we believe provide support for the use of maraviroc for treatment-experienced R5-tropic patients, a population whose pressing medical need brings with it a sense of urgency.

However, CCR5 inhibition is a novel therapeutic strategy and we recognize that additional questions around the use of CCR5 inhibitors for longer durations of therapy cannot be completely answered by the data we have presented here today and submitted for review.

[Slide]

A number of potential safety risks will require longer-term data within a broader population. These include the theoretical effects of CCR5 blockade on immune function and hepatic function, and the long-term effects of the switch to dual-tropic virus even transiently.

No data are currently available on the effects of maraviroc in the pediatric population, in pregnant women or in in utero exposed infants. As a result, Pfizer is committed to an extensive risk management plan to further assess these potential safety issues.

[Slide]

We have a number of projects in place or planned that will help us gather additional safety

data on maraviroc. These include the ongoing study in naive patients which will include five years of follow-up. The treatment-experienced studies that we presented today will continue for follow up for two years, with all-cause mortality out to five years. An expanded access program will provide data on maraviroc's safety in a broader patient population and a safety registry will collect specific safety endpoint information on patients prescribed maraviroc in routine clinical practice.

Collaborations with EuroSIDA and other cohort studies of HIV-infected patients will provide a reference for safety events occurring within the ongoing clinical program. We will also attempt to follow outcomes in maraviroc-exposed patients through large automated claims databases, most useful after significant uptake with maraviroc has been observed. We plan to initiate pediatric studies at the end of this year. With regard to in utero maraviroc exposure, infants exposed within Pfizer's clinical trials will, where possible, be enrolled into ongoing observational cohorts, and

post-approval the antiretroviral pregnancy registry will be utilized.

[Slide]

Based on data from adequate and well-controlled trials with 6-12 months of follow-up in treatment-experienced patients infected with an R5-tropic virus, we have demonstrated that maraviroc is effective in reducing viral load and increasing CD4 counts; that it is well tolerated with little evidence of effects related to postural hypotension; without adverse effects on hepatic function and without a significant increase in either malignancy or infections of concern. Treatment with maraviroc is not associated with an adverse outcome in patients with non-CCR5-tropic virus, and tropism changes in the presence of maraviroc were not associated with adverse effects.

[Slide]

While both the once and twice daily regimens demonstrated superiority over placebo, we believe that the 300 mg dose is preferred in order

to optimize therapy for patients with the lowest CD4 and highest viral load measurements. Because maraviroc is metabolized through the CYP3A4 system, in the presence of CYP3A4 inhibitors the dose should be reduced to 150 mcg BID. In the presence of CYP3A4 inducers the dose should be increased to 600 mg BID. At these doses therapy with maraviroc offers a favorable risk-benefit tradeoff for treatment-experienced patients identified by tropism assay to have an R5-tropic virus.

With that, we thank you for your attention.

DR. PAXTON: I would like to thank the presenters for keeping to time so we are actually 15 minutes ahead of time. So, we will be taking a 30-minute break and coming back at 10:15.

Before we leave, I just want to remind the committee to please refrain from conversations and interaction regarding today's meeting during the breaks. So, we will just have to talk about other things.

In terms of housekeeping, I believe the

bathrooms are located just right outside the doorways here. And, we will see you back here at 10:15. Thank you.

[Brief recess]

DR. PAXTON: All right, we are now ready to resume and we are now going to move into the FDA presentations so Scott Proestel, who is the medical officer in the Division of Antiretroviral Products, is going to be talking with us now about clinical efficacy and safety.

FDA Presentation

Clinical Efficacy and Safety

DR. PROESTEL: Good morning.

[Slide]

My name is Scott Proestel. I am a medical officer at the Food and Drug Administration in the Division of Antiretroviral Products, and I will be presenting the efficacy and safety data for maraviroc that was submitted in support of the NDA. I would like to certainly thank Dr. Susan Zhou of the Biometrics Division for assisting in the efficacy analyses.