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Jeffrey Murray, M.D., M.P.H.
Sarah Connelly, M.D.
Debra Birnkrant, M.D.
Kendall Marcus, M.D.

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P R O C E E D I N G S

Call to Order and Opening Remarks

DR. PAXTON: Good morning. This is the Antiviral Drugs Advisory Committee and we are here to discuss the first agent of the new pharmacological class of drugs, raltegravir, also known as MK-0518.

My name is Lynn Paxton. I am in the Epidemiology Branch of the Centers for Disease Control, Division of HIV-AIDS prevention, and I am here to welcome you all today. We are going to do a number of things. This is the call to order and the opening remarks, basically the welcome. We are going to be going on to give an introduction of the committee. Cicely Reese will then be reading the conflict of interest statement and then I have yet another statement that we will be reading to you before we actually start the meeting, and then we will move into the FDA introductory remarks by Dr. Kendall Marcus.

So, to move to the introduction of the committee I am going to start at that end of the

table. So, Dr. Havens, I would like you to begin the introductions.

Introduction of Committee

DR. HAVENS: I am Peter Havens, a pediatric infectious disease specialist at Children=s Hospital of Wisconsin and the Medical College of Wisconsin in Milwaukee. DR. FEINBERG: Judith Feinberg, infectious diseases, University of Cincinnati.

MS. SWAN: Tracy Swan, Hepatitis C/HIV Project Director, Treatment Action Group in New York.

DR. YARCHOAN: I am Bob Yarchoan. I am Chief of the HIV and AIDS Malignancy Branch and the AIDS Coordinator for the National Cancer Institute.

DR. GRANT: Robert Grant. I am a clinical virologist at the Gladstone Institute of Virology and Immunology and the University of California San Francisco.

DR. GLESBY: I am Marshall Glesby, infectious disease specialist at Weill Cornell Medical College.

DR. REESE: Cicely Reese, designated federal official.

DR. McGOWAN: Ian McGowan, professor of medicine at the University of Pittsburgh, Pennsylvania.

DR. ANDERSEN: Janet Andersen, statistician, Harvard School of Public Health.

DR. GORDIN: Fred Gordin, infectious disease specialist at the VA Medical Center here, in Washington, and George Washington University.

DR. MARCUS: Kendall Marcus, medical team leader, Division of Antiviral Products, FDA.

DR. CONNELLY: Sarah Connelly, medical reviewer at the FDA.

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

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

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

DR. PAXTON: Thank you very much. I think we will then go to the reading of the conflict of

interest statement by Cicely Reese.

Conflict of Interest Statement

DR. REESE: Thank you. 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 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 conflict of interest at this meeting.

We would also like to note a last minute cancellation by the committee=s non-voting industry representative, Dr. Eugene Sun. Dr. Sun has been invited to participate in the meeting on behalf of regulated industry. Dr. Sun is an employee of Abbott Laboratories.

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

DR. PAXTON: And we have one additional statement that I will read now to spare Cicely=s voice today: For topics such as those being discussed at today=s meeting there are often a variety of opinions, some of which are quite firmly held. Our goal at 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.

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 any conversations about today=s

topic take place in the open forum of the meeting and not during breaks or lunch. We are also aware that members of the media are anxious to speak with the FDA about these proceedings, however, like the advisory committee meetings, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

For the convenience of the media representatives, I would like to identify the FDA press contact. Mr. Chris Kelly, if you are present, would you stand? Thanks.

Finally, I would like to remind everyone present to please silence your cell phones and pagers if you have not already done so. And, we look forward to an interesting and productive meeting and thanks for your participation. Now we are going to have a presentation by Dr. Birnkrant.

DR. BIRNKRANT: Good morning, everyone. I just wanted to mention that three of our advisory committee members are rotating off as of October 31st, and they include Dr. Haubrich, Dr. Munk and Dr. Paxton. Given that Dr. Paxton is here with us

this morning, we would like to present her with a plaque in recognition and appreciation of her service to the agency, serving as a member of the Antiviral Drugs Advisory Committee and serving as its chair. Thank you, Lynn. We appreciate your help.

DR. PAXTON: Thank you. Thank you very much. I have a spot on my wall all ready.

At this time we are going to move to the FDA introductory remarks. Dr. Marcus?

FDA Introductory Remarks

DR. MARCUS: Good morning.

[Slide]

I would like to start by thanking the members of the advisory committee for their time and expertise on the issues to be discussed today.

[Slide]

The topic of today=s advisory committee is Isentress, also known as raltegravir, the first HIV integrase inhibitor to be submitted to FDA for NDA review.

[Slide]

Currently we have over 20 drugs from five classes available for treatment of HIV.

[Slide]

Drug development has greatly accelerated in recent decades.

[Slide]

We have drugs that target multiple steps in the process of HIV replication, including fusion, reverse transcriptase and protein cleavage. However, each of these classes have important limitations including resistance, toxicity and inconvenience. New drugs and new classes of drugs are needed to address the evolving challenges of HIV treatment.

[Slide]

Raltegravir is an integrase inhibitor, one of the promising new classes of antiretrovirals. Raltegravir blocks integration of HIV DNA into host DNA.

[Slide]

Today=s advisory committee focuses primarily on efficacy, safety and pharmacokinetic

data obtained from Phase 2 and 3 clinical trials. Importantly, week-16 primary endpoint data was accepted for submission of the NDA due to robust activity demonstrated in Phase 2 clinical trials.

[Slide]

Requests have been made to bring drug applications for new molecular entities for review with advisory committees. For today=s agenda, Merck will first present an overview of their clinical development program. FDA will follow with a summary of important highlights of their review.

[Slide]

The advisory committee will then be asked to address the adequacy of submitted data, any potential concerns and clinical trial design issues.

[Slide]

Before we begin our presentations I would like to thank members of the FDA review team for their timely and thorough review of this application. Thank you.

DR. PAXTON: We are now going to move into

the applicant presentations by Merck. I believe it is Dr. Fromtling who will be giving the presentation today.

Applicant Presentation - Merck & Co., Inc.

Introduction

DR. FROMTLING: Thank you, Dr. Paxton and good morning.

[Slide 1]

Merck is pleased to participate in today=s FDA Antiviral Drugs Advisory Committee meeting to discuss raltegravir, Merck & Co.=s first-in-class HIV integrase inhibitor for the treatment of Human immunodeficiency virus infection.

[Slide 2]

I am Dr. Robert Fromtling, from regulatory affairs, and I will provide a brief introduction of raltegravir, also known as MK-0518. Dr. Bach-Yen Nguyen, from clinical research, will then provide a background of the raltegravir program, an overview of the clinical development program and the clinical trial results. Dr. Robin Isaacs, from clinical research, will discuss the drug-drug

interaction studies that have been conducted with raltegravir, as well as an overview of the risk management plan proposed by Merck & Co. Dr. Isaacs will finish by providing the conclusions of our presentation this morning.

[Slide 3]

In the United States in 2005, there were an estimated 1.2 million HIV-positive people, including 33,000 new infections and more than 16,000 AIDS deaths. The unmet medical need for new therapeutic agents is further justified by data showing that approximately 10-15 percent of treated patients are failing therapy and have triple-class resistant HIV. Current regimens in treatment-experienced patients often have issues with safety and/or inconvenient dosing options. Ideally, new agents should demonstrate potent efficacy, favorable safety profile and dosing convenience and manageable drug interactions. There is an urgent need in the heavily treatment-experienced population.

[Slide 4]

Raltegravir is a significant advance in HIV therapy and addresses this unmet medical need. Raltegravir has a novel mechanism of action. It is a first-in-class HIV integrase inhibitor with no cross-resistance with currently licensed antiretroviral agents.

In clinical trials, raltegravir demonstrated rapid, potent and sustained antiretroviral activity in treatment-experienced patients. Raltegravir represents a major contribution to the new treatment paradigm. Undetectable viral load has been demonstrated in treatment-experienced patients with triple-class resistant virus.

Raltegravir also has an excellent safety profile and tolerability. It has a low pill burden and convenience in dosing. It is dosed one tablet twice daily without regard to food, and no dose adjustment with other antiretroviral agents is needed. Overall, raltegravir has a favorable benefit/risk profile, particularly in treatment-experienced patients.

[Slide 5]

The recommended or proposed indication and dosage and administration for raltegravir follows. The proposed indication is that raltegravir is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The proposed dosage and administration is that the recommended dosage of raltegravir is 400 mg administered orally twice daily with or without food. Raltegravir is to be given in a combination regimen with other antiretroviral agents.

[Slide 6]

Today we have several consultants with us at the advisory committee meeting. They are Dr. Terry Blaschke from Stanford University, Dr. Susan Krown from Memorial Sloan Kettering Cancer Center, Dr. Martin Markowitz from the Aaron Diamond AIDS Research Center, Dr. Robert Maronpot from Maronpot Consulting, Dr. Alexander Walker from i3 Drug

Safety and Dr. L-J Wei from Harvard University.

[Slide 7]

At this time I would like to introduce Dr. Bach-Yen Nguyen, from clinical research, who will begin by providing the background for raltegravir. Thank you for your attention. Dr. Nguyen?

Raltegravir Background

DR. NGUYEN: Good morning. This presentation will provide you with the relevant background of raltegravir, an overview of the clinical development program, and a detailed review of the clinical trial results on efficacy, resistance and safety.

[Slide 8]

This cartoon shows the HIV life cycle and the various targets for therapeutic intervention.

[Slide 9]

As mentioned by Dr. Marcus earlier, the approved antiretorviral agents belong to one of the four classes.

[Slide 10]

The nucleoside and non-nucleoside reverse

transcriptase inhibitors, both inhibiting the reverse transcription of RNA--

[Slide 11]

--the protease inhibitors inhibiting the cleavage of the transcribed proteins and the entry inhibitors, including the fusion inhibitors and CCR5 antagonists which interfere with the process of viral entry.

[Slide 13]

The HIV integrase enzyme represents a novel target for therapy. It catalyzes the integration of viral DNA into host DNA, a critical step required for HIV replication. Integration of viral DNA into host DNA is a mufti-step process. In the next slide I will show you the details of integration and the mechanism of action of raltegravir.

[Slide 14]

After reverse transcription of viral DNA the integrase enzyme binds to the viral DNA at specific sequences, known as long terminal repeats, and forms the viral integration complex.

[Slide 15]

In the preintegration complex the integrase enzyme catalytically processes each of the 3' ends of the viral DNA. The preintegration complex is then imported into the nucleus where the enzyme binds viral DNA and host DNA in an irreversible step known as strand transfer.

[Slide 16]

This is followed by repair of the integrated product by host enzymes. Raltegravir blocks the last step of integration, the strand transfer step, resulting in degradation of the viral DNA or production of certain products which end the HIV replication cycle.

[Slide 17]

Raltegravir has demonstrated potent in vitro activity with an IC_{95} of 31 nM in the presence of human serum. It is active against multi-drug resistant virus. It is also active against CCR5 and CXCR4 viruses. Of importance, the HIV strains that become resistant to raltegravir remain sensitive to other approved antiretroviral agents.

Additive or synergistic effect has been demonstrated in vitro with nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors and enfuvirtide. Raltegravir is not genotoxic in in vitro and in in vivo assays.

[Slide 18]

The pharmacokinetics of raltegravir were extensively characterized in several clinical studies and support twice daily dosing. The terminal half-life is approximately nine hours, with a shorter alpha-phase half-life of one hour. There was a slight degree of accumulation of $C_{12\text{-hour}}$ at trough with multiple dosing.

There was considerable variability in the pharmacokinetics of raltegravir. In Phase 1 studies doses as high as 800 mg twice daily were generally well tolerated. At the dose of 100 mg twice daily the mean trough exceeds the IC_{95} in the presence of human serum. The pharmacokinetics are similar across gender, race, age in adult patient populations, HIV infection status, hepatic and renal function and body mass index.

[Slide 19]

Raltegravir is rapidly absorbed, with a T_{max} achieved in approximately three hours. Based on early Phase 1 studies which did not demonstrate a significant food effect, Phase 2 and 3 studies were conducted with dosing without regard to food. With the final market formulation study raltegravir exposure was similar with a high-fat meal and fasting state. However, high-fat meals appear to slow the rate and extend duration of absorption, with an approximate 7.4 hour delay in T_{max}, a 34 percent decrease in C_{max} and 8.5-fold increase in $C_{12\text{-hour}}$. Raltegravir is metabolized primarily via glucuronidation, mediated by UGT1A1. There was minor renal elimination.

Clinical Development Program Overview

[Slide 20]

Before reviewing the results from the clinical trials, I would like to provide you with an overview of the clinical development program. The objective was to demonstrate that raltegravir is safe and efficacious in the treatment of HIV

infection, particularly in treatment-experienced patients.

[Slide 21]

Eighteen Phase 1 studies were conducted in 315 healthy subjects to characterize the safety, pharmacokinetics, food effect and relevant drug-drug interactions to support the Phase 2 and 3 program.

[Slide 22]

The first Phase 2 dose finding study was in treatment-naive patients, where raltegravir was evaluated at four different doses given as monotherapy for ten days, to establish proof of concept prior to evaluation of raltegravir in combination therapy in part 2.

[Slide 23]

The second dose-finding study was in 179 treatment-experienced patients failing therapy with triple-class resistant virus.

[Slide 24]

Based on favorable Phase 2 safety and efficacy data, the Phase 3 program was initiated

with two identical studies in 702 treatment-experienced patients failing therapy with multi-drug resistant virus to confirm the results of Phase 2. The regulatory submission in April, 2007 includes complete week-16, and approximately 60 percent of patients who had complete week-24 data from the Phase 3 studies, along with 40-week data from the two Phase 2 studies. All Phase 2 and 3 studies are ongoing to accumulate more data.

[Slide 25]

In addition, we have initiated a worldwide expanded access program of a Phase 3 study in treatment-naive patients, a pediatric study, two Phase 3 studies in patients who have virologic control on a Kaletra regimen to evaluate the switch to a raltegravir-containing regimen.

Clinical Trial Results: Efficacy, Resistance and Safety

[Slide 26]

The last part of my presentation will be the review of the clinical trial results. We will focus on the Phase 3 data after a brief summary of

the Phase 2 findings.

[Slide 27]

As you recall from the clinical development program overview, there were two Phase 2 dose-ranging studies. In the treatment-naive study, protocol 004, raltegravir was evaluated at four different doses of 100, 200, 400 and 600 mg twice daily versus efavirenz or in combination with tenofovir and lamivudine. In the treatment-experienced protocol, 005, raltegravir was evaluated at doses of 200, 400 and 600 mg twice daily versus placebo, or in combination with optimized background therapy selected by investigators based on baseline resistance testing and prior treatment history. In Phase 2 no investigational drugs such as tripanavir and darunavir were allowed in optimized background therapy.

[Slide 28]

This shows the efficacy results observed in the Phase 2 treatment-experienced study, protocol 005. Since you will see similar figures

later in the presentation I would like to spend a minute going over the organization of the figure. The X axis shows the study weeks. The measure shows the number of patients contributing data from the different treatment groups. In this non-completer, equal to failed analysis all randomized patients were accounted for at each time point since discontinuations were counted as virologic failures. The You axis shows the efficacy measurement which, in this case, is the percent of patients achieving viral RNA less than 400 copies/mL. The bar at each time point shows the 95 percent confidence intervals.

I would like to point out that when 400 mg twice daily was selected as the Phase 3 dose the protocol was amended so all patients could switch to receive open-label raltegravir 400 mg twice daily after having reached at least week 24, the primary time point. Between week 24 and 48 patients, including the six who still remained on placebo, were switched to receive open-label raltegravir 400 mg twice daily. By week 48,

greater than 85 percent of the patients were receiving open-label raltegravir or discontinued randomized therapy.

[Slide 29]

Now let=s concentrate on the results. The data here demonstrate that for all raltegravir with optimized background therapy groups there was rapid, antiretroviral effect, with approximately 70 percent of patients achieving viral RNA less than 400 copies/mL at week 24 which was sustained out to week 48. There was no dose differentiation among the raltegravir groups.

In contrast, in the placebo control with optimized background therapy only 26 percent of patients had HIV RNA less than 400 copies/mL at week 24. The treatment difference between raltegravir groups and the placebo with optimized background therapy alone is highly statistically significant, with a p value of less than 0.001.

The superior antiretroviral effect of raltegravir with optimized background therapy versus optimized background therapy alone was also

demonstrated with all the efficacy endpoints including the percent of patients achieving viral RNA less than 50 copies/mL and change from baseline in CD4 cell counts.

The results from the second Phase 2 dose-ranging study in treatment-naive patients also showed no differentiation of doses based on efficacy or safety through 48-week data. So, in both protocols all doses studied demonstrated potent and sustained efficacy, with no dose-limiting toxicities even in patients receiving raltegravir at the highest dose of 600 mg twice daily in the presence of drugs that increase the plasma level of raltegravir, such as tenofovir and atazanovir. There were no dose-related toxicities. Extensive pharmacokinetic/pharmacodynamic analyses did not identify a relationship between raltegravir pharmacokinetic parameters and treatment outcomes. Based on Phase 2 data pharmacokinetic/pharmacodynamic analyses for raltegravir doses studied in combination regimens were likely the plateau of the dose-response curve.

Based on this result, the dose of 400 mg twice daily was selected as the Phase 3 dose. This is the highest dose that would provide a margin for safety and efficacy when raltegravir is co-administered with drugs that are inhibitors or inducers of UGT1A1 respectively. Data from drug interaction studies will be discussed later by Dr. Isaacs.

[Slide 30]

The Phase 3 program is comprised of two identical studies which are randomized, double-blind, placebo-controlled studies with data and safety monitoring board. The primary analysis was at week 16. These studies enrolled HIV-infected patients failing therapy with triple-class resistant virus with a viral load of greater than 1,000 copies/mL.

In the Phase 3 program the inclusion criteria were less stringent than in Phase 2 in order to provide a real-world assessment of the efficacy and safety of raltegravir. Thus, there was no CD4 cell count cut-off and patients with

stable hepatitis B and hepatitis C co-infection, patients with elevated liver function tests up to five times the upper limit of normal, as well as patients with stable malignancies not requiring chemotherapy at study entry were allowed in the studies.

Protocol 18 enrolled patients in Europe, Asia/Pacific and Peru. Protocol 19 enrolled 351 patients in North and South America. In each study patients were randomized at a 2:1 ratio to receive either raltegravir 400 mg twice daily or placebo in combination with optimized background therapy. Optimized background therapy was selected by investigators based on baseline resistance testing and prior treatment history. Darunavir and tipranavir, which were investigational at that time, were permitted in optimized background therapy in order to construct the most optimal regimen for patients.

[Slide 31]

The primary efficacy endpoint is the percent of patients achieving viral RNA less than

400 copies/mL at week 16. The key secondary endpoints include the most stringent end, percent of patients achieving viral RNA less than 50 copies/mL at week 16 in addition to change from baseline in CD4 cell counts. Patients with confirmed virologic failure after at least 16 weeks of double-blind therapy could enter the open-label post-virologic failure raltegravir arm. These patients were considered virologic failures in the analysis.

[Slide 32]

In both protocols the definition of virologic failure includes non-responders and virologic relapse. Non-responders are patients who have less than one log drop in HIV RNA from baseline or HIV RNA greater than 400 copies/mL at week 16. Virologic relapse is defined as having greater than one log increase in HIV RNA above the nadir, or HIV RNA greater than 400 copies/mL after initial response of less than 400 copies/mL.

To characterize the activity of antiretroviral therapies and optimized background

therapy the genotypic and phenotypic sensitivity score based on the results of the PhenosenseGT resistance assay at baseline was used. For each active drug in optimized background therapy +1 was added to the score. For enfuvirtide +1 was added to the score for use in enfuvirtide-naive patients since there was no clear clinical cut-off for resistance testing. For darunavir, since reports on sensitivity were not available at that time, +1 was added to the score for use in darunavir-naive patients.

[Slide 33]

The patient disposition in both studies is summarized in this slide. In each study approximately 500 patients were screened and about 350 got randomized. The major reasons for non-randomization were screening failure with viral load below the study cut-off of 1000 copies/mL or no documentation of triple-class resistant virus.

[Slide 34]

In each study patients were randomized to receive either raltegravir or placebo at a 2:1

ratio. Only two patients in each study did not receive treatment. Most patients in the raltegravir groups continued on double-blind therapy but there were more discontinuations in the placebo group in each of the studies due to virologic failure.

[Slide 35]

However, these patients did not get lost to follow up since they entered the open-label post-virologic failure treatment group. They were counted as failures in the primary efficacy analysis but continued to contribute to the safety database. There were very few discontinuations due to adverse experiences. For both studies we have follow up in 97 percent of treated patients. Please keep in mind the 2:1 randomization ratio for raltegravir and placebo and the patients switching to open-label post-virologic failure arm since that means an imbalance in patient-year exposure when comparing raltegravir with placebo. This will become relevant when we discuss safety.

[Slide 36]

The baseline characteristics of age, gender and race were comparable between the two treatment groups. The baseline disease characteristics were also comparable between the two treatment groups within each study. The majority of these patients had advanced disease with AIDS and extensive prior therapy. As mentioned earlier, patients with hepatitis B and C co-infection were allowed in both studies. There were more patients with hepatitis B co-infection in the raltegravir group than in the placebo control group in both studies but overall all factors were fairly well balanced between the two different treatment groups in each of the studies.

[Slide 37]

Given that the optimized background therapy is heterogeneous, it is important to characterize the number of active antiretroviral agents with the GSS and PSS score at baseline. Patients who had GSS and PSS of zero represent those with the most limited treatment options. In both studies, approximately 20-30 percent of

patients had GSS of zero and approximately 10-19 percent of patients had PSS of zero. For many patients in these studies the virus is also susceptible to enfurvitide and darunavir. In both studies the years of enfurvitide as first used in optimized background therapy was approximately 20 percent and the years of darunavir was approximately 25-50 percent.

[Slide 38]

This slide and the next one show the results from the primary efficacy analysis evaluating percent of patients achieving viral RNA less than 400 copies/mL. The X axis shows the study weeks. The legend shows the number of contributing patients in this non-completer, equal to failure analysis. All patients have week 16, the primary time point. Approximately 60 percent of patients have week 24 data. The You axis shows the percent of patients with HIV RNA less than 400 copies/mL. The bars show the 95 percent confidence interval intervals. Raltegravir with optimized background therapy is in yellow and the placebo

control with optimized background therapy is in white.

Similar to Phase 2 data, for the raltegravir group there was rapid, important antiretroviral effect with 77 percent of patients achieving viral RNA less than 400 copies/mL at week 16, which was sustained out to week 24. This is in contrast to only 41 percent of patients receiving optimized background therapy alone. The better response rate observed in the control group compared to Phase 2 data reflects the availability of the use of more active optimized background therapy. Raltegravir with optimized background therapy was superior to optimized background therapy alone, and the treatment difference at week 16 was highly statistically significant, with a p value of less than 0.001.

[Slide 39]

Similar results were observed in the second Phase 3 study. In protocol 19 all patients had week-16 data and approximately 60 percent of patients had week-24 data in this non-completer,

equal to failure analysis. With the raltegravir group there was rapid and potent antiretroviral effect with 77 percent of patients achieving viral RNA less than 400 copies/mL at week 16 which was sustained out to week 24, in contrast to 43 percent of patients receiving optimized background therapy alone. The treatment difference at week 16 is highly statistically significant, with a p value of less than 0.001.

[Slide 40]

Each of the Phase 3 studies has demonstrated superior efficacy of raltegravir with optimized background therapy versus optimized background therapy alone in the primary efficacy analysis using the primary efficacy endpoints. Similar results were demonstrated with all secondary efficacy endpoints, including the percent of patients achieving viral RNA less than 50 copies/mL and change from baseline in CD4 cell counts. Given that both studies are identical in design, integrated analysis of efficacy using combined data was also performed to confirm the

superior efficacy of raltegravir and demonstrate the consistent treatment effect of raltegravir in different subgroups.

[Slide 41]

This integrated analysis evaluated three different efficacy endpoints, percent of patients achieving viral RNA less than 400 copies/mL, percent of patients achieving viral RNA less than 50 copies/mL and change from baseline in CD4 cell count. Regardless of the efficacy endpoint, raltegravir with optimized background therapy consistently demonstrated superior efficacy compared to placebo with optimized background therapy at week 16 which was sustained out to week 24.

The first figure on the left shows 77 percent of patients in the raltegravir group achieving viral RNA less than 400 copies/mL versus 42 percent in the control group. The figure in the middle shows 62 percent of patients in the raltegravir group achieving viral RNA less than 50 copies/mL versus 35 percent in the control group.

The last figure shows an increase of 84 CD4 cell counts from baseline in the raltegravir group versus 36 in the control group. The next slide shows the results of separate analyses by important prognostic factors and baseline demographics.

[Slide 42]

All of these slides have similar formatting. The prognostic factors are indicated on the left. The number of patients contributing data is under the N column. Raltegravir with optimized background therapy is represented as the yellow bar and the placebo with optimized background therapy is the white bar. The number at the end of each bar represents the percent of patients achieving viral RNA less than 400 copies/mL at week 16. The results here demonstrated that regardless of baseline viral load and baseline CD4 cell count, raltegravir consistently demonstrated better efficacy than the control group.

[Slide 43]

The number of active antiretroviral agents

in optimized background therapy as measured by GSS is another important prognostic factor. A separate efficacy analysis by GSS of optimized background therapy was undertaken. On the left you can see the different subgroups of GSS. Regardless of the GSS, the raltegravir group consistently demonstrates better efficacy than the control group. Of note, the treatment difference between raltegravir and control group is largest in those with GSS of zero, favoring raltegravir. However, it is important to point out that with more active optimized background therapy 85-89 percent of patients in the raltegravir group had HIV RNA less than 400 copies/mL. Similar results were observed with the subgroup analysis with PSS.

[Slide 44]

As mentioned earlier, new and active antiretroviral drug therapy such as enfuvirtide and darunavir are important prognostic factors. Subgroup efficacy analyses by use of these selected antiretroviral agents as first used in the optimized background therapy were performed. The

subgroups, as indicated on the left, included patients who had first use of both enfuvirtide and darunavir in optimized background therapy; those who had first us of enfuvirtide; those who had first use of darunavir; and those who used neither in optimized background therapy.

Regardless of the use of these selected antiretroviral agents, the raltegravir group consistently demonstrated better efficacy than the control group. The treatment difference is greatest when neither enfuvirtide nor darunavir was used in optimized background therapy, favoring the raltegravir group. However, the best virologic response was observed when either enfuvirtide or darunavir was first used in optimized background therapy with 90 percent or greater achieving viral RNA less than 400 copies/mL at week 16. This is remarkable given that these patients had triple-class resistant virus.

[Slide 45]

This slide shows the results of the subgroup analyses by gender, race, region and viral

subtype. The format is different from previous slides to show treatment differences between raltegravir and placebo across multiple subgroups and multiple efficacy endpoints. The efficacy measurements include percent of patients achieving viral RNA less than 400 copies/mL, percent of patients achieving viral RNA less than 50 copies/mL and change in CD4 cell count from baseline at week 16.

Unlike in previous slides, the results show not the absolute response but the treatment difference between the raltegravir and the control groups with the 95 percent confidence interval. If the treatment difference between the raltegravir and the placebo control group is greater than zero to the right of the vertical line, it favors raltegravir. If the treatment difference is less than zero to the left of the vertical line, it favors placebo. The results demonstrated that regardless of the subgroup raltegravir efficacy was consistently better than that of the control group by all of these efficacy endpoints.

[Slide 46]

In conclusion, in HIV-infected patients failing therapy with triple-class resistant virus, raltegravir at 400 mg twice daily plus optimized background therapy has demonstrated rapid, potent and superior antiretroviral and immunological efficacy compared to placebo with optimized background therapy.

In patients receiving new, active antiretroviral agents in optimized background therapy, such as enfuvirtide and/or darunavir, 90 percent or greater achieved viral RNA less than 400 copies/mL. The treatment effect of raltegravir is consistent regardless of prognostic factors and baseline demographics. Raltegravir has demonstrated sustained efficacy in patients followed out to week 48 in Phase 2 studies.

[Slide 47]

In addition to the evaluation of efficacy, we also have ongoing evaluation of raltegravir resistance to determine the genotypic marker of raltegravir resistance in patients with virologic

failure and understand how to best use the drug. The next three slides summarize the results of this ongoing evaluation.

[Slide 48]

In patients with triple-class resistant virus, virologic failure on raltegravir was observed in 38 patients in protocol 005. Genotypic data were available for all of these 38 failures and demonstrated that most patients failing raltegravir had integrase mutations conferring raltegravir resistance. Most of these mutations were in either of the two genetic pathways N155 or Q148. Resistance was typically associated with two or more mutations, with the Q148H/G140S being most common. There was no association between dose and/or drug concentration and resistance. Partial genotype data available for Phase 3 protocols showed similar findings.

[Slide 49]

These data show that integrase mutations associated with raltegravir virologic failure confer raltegravir resistance. In in vitro assays

a single mutation at amino acid 155 or 148 confers 13 to approximately 44 resistance. The addition of mutation E92Q/N155H increases resistance from 13-fold to 64-fold, and the addition of mutation G140S to Q148H or R increases resistance to more than 400-fold. Thus, multiple mutations engender higher-level resistance than single mutation.

[Slide 50]

This slide summarizes our current understanding of raltegravir resistance and the clinical implication. In patients failing raltegravir the HIV isolate often displayed integrase mutations conferring raltegravir resistance. The signature integrase mutations Q148 and N155 as individual mutations confer reduced susceptibility and reduced viral replication capacity. Resistance of more than one mutation is needed to engender high-level resistance. There was no association between dose and/or drug concentration and resistance. Additional resistance analyses are ongoing.

The Phase 2 efficacy data demonstrate that

suppression of HIV RNA to undetectable is achievable through week 48 in patients with triple-class resistant virus. Thus, it is very important to identify the factors associated with development of resistance associated with virologic failure to maximize the antiretroviral effect of raltegravir.

[Slide 51]

Factors that decrease the likelihood of developing resistance include low viral load, first use of active antiretroviral agents in optimized background therapy and active optimized background therapy with PSS and GSS greater than zero. These data are consistent with the notion that function of monotherapy increases the likelihood of treatment failures and development of resistance. Therefore, raltegravir should be used in combination with other potent agents to maximize its clinical benefits.

[Slide 52]

Now I would like to go on to the results of the safety analysis.

[Slide 53]

Before getting into the details of the safety data, let me briefly update you with the total number of patients receiving raltegravir at the recommended dose of 400 mg twice daily or higher during the double-blind and open-label phases in the Phase 2 and 3 studies. As you can see, we have over 400 patients receiving at least 24 weeks of therapy and over 100 patients receiving at least 48 weeks of therapy at doses of 400 mg twice daily or higher.

[Slide 54]

This slide summarizes the extent of the Phase 2 and 3 safety database which includes a total of 878 patients treated with any dose of raltegravir in Phase 2 and 3 from the double-blind, open-label post-virologic failure and open-label extension treatment groups.

[Slide 55]

The primary focus is on the double-blind phase which has a control group. The primary analysis includes treatment-experienced patients

receiving the proposed dose of 400 mg twice daily in protocols 5, 18 and 19. This included 507 patients on raltegravir, with 261 patient-years of exposure, versus 282 patients on placebo, with 127 patient-years of exposure.

[Slide 56]

For the complete evaluation of malignancies, which will be discussed later on, we also included patients receiving all the doses of raltegravir and all patient populations including treatment-naive patients. That included 758 patients on raltegravir versus 323 on control.

[Slide 57]

In addition to the double-blind cohort, we also evaluated safety of raltegravir in the open-label, post-virologic failure cohort and open-label extension which included another 120 patients receiving raltegravir. With this background exposure, let=s look at the safety data.

[Slide 58]

In Phase 1 studies raltegravir was generally well tolerated in healthy subjects. In

both dose-ranging studies in treatment-naive and treatment-experienced patients raltegravir was generally well tolerated, with a safety profile similar to the control groups. Of note, there were no dose-limiting toxicities with doses up to 600 mg twice daily in the presence of drugs that increase the plasma level of raltegravir, such as tenofovir and atazanovir. There were no dose-related toxicities. In treatment-naive patients there was no impact on lipid levels.

[Slide 59]

Now let=s review the data from the integrated summary of safety of treatment-experienced patients receiving the proposed dose of 400 mg twice daily in protocols 5, 18 and 19 in the double-blind phase.

[Slide 60]

This is the overall summary of the clinical adverse experience of the double-blind phase which included 507 patients in the raltegravir group and 282 patients in the control group. In this slide and in subsequent slides

drug-related adverse experience refers to those determined by the investigator to be possibly, probably or definitely related to any drug in the regimen. That includes raltegravir, or placebo alone, or in combination with optimized background therapy, or optimized background therapy alone.

The results here demonstrate that the incidence of adverse experiences was comparable between the raltegravir and the control groups. Despite a very sick patient population, the incidence of serious drug-related adverse experiences, of death and adverse experiences leading to discontinuations was very low. The incidence of serious adverse experiences was comparable between the two treatment groups. However, in the original application there were more reports of malignancies in the raltegravir group and this will be discussed in detail later.

[Slide 61]

This shows the profile of the drug-related clinical adverse experiences of any intensity from the double-blind phase with an incidence of at

least two percent in any treatment group. On the left-hand side is the list of ten drug-related clinical adverse experiences. The injection site reaction was due to enfurvitide. For each of the drug-related clinical adverse experiences the incidence was generally comparable between the raltegravir and the control groups.

[Slide 62]

If you focus only on the moderate and severe intensity drug-related clinical adverse clinical experiences with an incidence of at least two percent there were very few, which occur in less than four percent of patients in either treatment group.

[Slide 63]

In addition to clinical adverse experiences, we also evaluated laboratory adverse experiences which were lab abnormalities that were considered by the investigator to be adverse experiences. There were few drug-related lab adverse experiences and the incidence was low for both raltegravir and placebo control groups. In

general, these lab adverse experiences were transient and did not lead to discontinuations. To understand the slightly higher percent of patients with elevated serum ALT and AST in the raltegravir group we also looked at the lab abnormalities using the more objective Division of AIDS toxicity criteria.

[Slide 64]

This displays the incidence of grade 2, 3 and 4 lab abnormalities for serum bilirubin, AST, ALT and alkaline phosphatase. The grading criteria are in the second column. Overall, the incidence of grade 3 and 4 abnormalities was low and generally comparable between the raltegravir and the control group. Most of grade 2, 3 and 4 elevated bilirubin was isolated hyperbilirubinemia associated with concomitant use of atazanovir or indinavir. In addition to the liver function tests, we also evaluated all the lab parameters, including common hematological laboratories and serum chemistry, and the incidence of grade 3 and 4 abnormalities was low and generally comparable

between the two treatment groups.

[Slide 65]

In order to be as comprehensive as possible in our assessment of transaminase and bilirubin laboratory values, we performed a Hy=s Law analysis based on the data in the double-blind phase. Hy=s Law is a prognostic rule to assess drug-induced hepatotoxicity. The criteria, as outlined here, are consistent with those applied by the FDA during the recent advisory committee. It is important to note that Hy=s Law aims to evaluate markers of hepatic cell injury in the absence of coexisting confounding clinical conditions. In this evaluation no patients met the criteria of Hy=s Law. As has been noted earlier, patients enrolled in the raltegravir studies were severely immunodeficient; often had multiple AIDS diagnosis; could be chronic hepatitis B and C co-infected; and were receiving numerous concomitant medications, both antiretroviral agents and other therapeutic classes. Furthermore, some commonly used antiretroviral agents, such as atazanovir and

indinavir cause isolated hyperbilirubinemia. Despite this, four patients in the raltegravir groups met the biochemical criteria for Hy=s Law and in all of these cases significant confounding factors were present.

In the first case the patient had elevated bilirubin associated with atazanavir use and a transient increase in transminases that resolved with continued raltegravir therapy.

The second case was due to hepatitis B virus reactivation when tenofovir was inadvertently stopped, which resolved with reintroduction of tenofovir and the patient continued raltegravir therapy.

In the third case a patient was stable with chronic hepatitis C had a transient biochemical disease flare which resolved with continued raltegravir therapy.

Finally, the last case was a very complicated case in which a highly immunodeficient patient, who began indinavir therapy at the same time as raltegravir, developed two episodes of

hepatitis, the first in the setting of acute thyrotoxicosis and acute respiratory syndrome and the second in the setting of bronchopneumonia which ultimately led to septic shock an death.

Overall, in all four of these cases there were significant clinical confounders present. Thus, Hy=s Law was not met in any of the raltegravir-treated patients.

[Slide 66]

Safety evaluation in special groups by intrinsic and extrinsic factors was also conducted. Raltegravir demonstrates a similar safety profile regardless of race, gender and age in the adult patient population up to 65 years old.

In regard to extrinsic factors, the raltegravir safety profile was not affected when used in combination with atazanavir and/or tenofovir which increase the level of raltegravir.

The safety profile in patients with hepatitis B and C co-infection was similar to that in patients without co-infection. It is worth noting that the rates of AST and ALT abnormalities

were somewhat higher in the subgroup with hepatitis B and C co-infection but this was observed for both the raltegravir and the placebo control groups. In addition to the double-blind phase, we also reviewed the safety information from the open-label groups. The safety profile of raltegravir was generally comparable to that observed in the double-blind data. Based on this comprehensive review, raltegravir demonstrates a favorable safety profile, comparable to placebo, in combination with optimized background therapy. The two-month safety updated report, repeating the safety analysis presented in the original application, confirms this conclusion.

[Slide 67]

As mentioned earlier, there were more reports of malignancies in patients receiving raltegravir at the time of the original application. The remainder of this presentation will review these cases of malignancies in detail.

Given the imbalance in the number of malignancies in the raltegravir group in the

original application, a comprehensive review was undertaken and the results were promptly communicated to the DSMB, FDA, investigators, patients and scientific community in public presentations. To evaluate this finding, a primary focus was on data from the double-blind period where there were comparative data.

The primary population includes all patients receiving any dose of raltegravir in the double-blind period of Phase 2 and 3 studies. The raltegravir group included 758 patients with 508 patient-years of exposure. The comparator group included 323 patients with 169 patient-years of exposure. First, there were threefold more exposures in the raltegravir group versus the comparator group. The details of the cases will be discussed in the next slide.

To provide the advisory committee with the most updated data, we also have obtained permission from the agency to provide results of our updated review based on all information through July 9th, 2007 which is under review by the agency. This

updated review evaluates the same studies with the same patient population, using the same analysis method. There was approximately 60 percent greater exposure time to study medications than in the original application, and 820 patient-years in the raltegravir group versus 261 patient-years in the control group. As you will see shortly, the imbalance in the number of malignancies has not been sustained with additional exposure.

[Slide 68]

Before discussing the rates and the relative risk I would like to share with you the details of the malignancies first. This slide summarizes the profile of the malignancies reported in the original application. The next slide will show you the cumulative cases from the updated review.

As noted previously, there were threefold more patient-years of exposure in the raltegravir than the comparator group. In the raltegravir group there were ten patients with reports of malignancies. Three of these ten cases were

previously diagnosed malignancies. Nine of ten occur within the first three months of therapy suggesting that these cases were likely present at study entry. The types of malignancies were those that have been described in the AIDS patient population. Half of them were AIDS-defining malignancies. As noted in the briefing document, the rates of all these malignancies were comparable to those reported in patients with AIDS. The patients with reports of malignancies on raltegravir were severely immunodeficient. Sixty percent had CD4 cell counts less than 50 cells at study entry. In the comparator group there was only one patient with squamous cell carcinoma of the vocal cord.

[Slide 69]

This shows the cumulative number of malignancies from the updated data. There is approximately 60 percent more exposure with 820 patient-years in the raltegravir group and 261 patient-years in the comparator group. With this increased exposure, there were more cases reported

for both the raltegravir group and the control group. Compared to data in the original application, in the raltegravir group you see the same types of malignancies. As noted previously, several were recurrences of previously diagnosed cancers. In the comparator group there were five cases reported and the types were similar to those reported for the raltegravir group.

[Slide 70]

Now that you have seen the details of the malignancies, I would like to summarize the rates and the relative risk observed both in the original application and the updated data. Both sets of analyses include the same patient population from the same studies. In the original application, in the raltegravir group there were 10 patients with over 508 patient years of exposure, a rate of 2.0 per 100 patient-years. This is in comparison to one case over 169 patient-years of exposure, or the rate of 0.6 per 100 patient-years. The relative risk was 3.3 and a very wide confidence interval.

In the updated review there was a

significant increase in the exposure, by 60 percent, for both treatment groups. The updated data showed that the rates of malignancies were comparable between the two treatment groups. In the raltegravir group the rate was 2.3 per 100 patient-years versus 2.9 per 100 patient-years in the comparator group, with a relative risk of 1.2 with a much tighter confidence interval. Thus, with increased exposure the new data allows us to evaluate the risk with more precision.

[Slide 71]

In summary, in the original application an imbalance in the number of malignancies was noted in the raltegravir group. After a thorough review of all of these cases, no specific cancer risk attributable to raltegravir is apparent. The malignancy types are those anticipated in the AIDS patient population. The rates in the raltegravir group are consistent with those seen in severely immunodeficient AIDS patient population, as discussed in the briefing document. Many of the malignancies were likely present at time of study

entry or were recurrences of prior diagnosed malignancies. Based on the most up to data analysis, the imbalance in the number of malignancies submitted in the original application has not been sustained with more substantial follow up. The current data are limited. Thus, further follow-up measures are planned, as will be described later on by Dr. Isaacs.

[Slide 72]

In conclusion, in patients with advanced HIV-1 infection, failing antiretroviral drug therapies with multi-drug resistant virus, raltegravir in combination with optimized background therapy was generally well tolerated, with no dose-limiting toxicities. The safety profile was comparable to that of placebo with optimized background therapy. Raltegravir was well tolerated in patients regardless of age, race, gender and in patients with hepatitis B and/or C co-infection. It is important to note that there were very few adverse experiences leading to discontinuation in this very sick patient

population.

[Slide 73]

This completes the detailed review of the clinical trial results. Now I would like to hand this over to Dr. Isaacs who will complete the Merck presentation. Thank you very much for your attention.

Drug-Drug Interactions, Risk Management Plan and Conclusions

DR. ISAACS: Dr. Nguyen has provided a summary of the clinical evaluation of raltegravir and has provided strong evidence that raltegravir is efficacious and is generally well tolerated in heavily treatment-experienced patients. In this last section of the presentation I will first discuss raltegravir=s drug-drug interaction profile and why no dose adjustment of raltegravir is required when it is co-administered with other antiretroviral agents. Then I will review the proposed risk management plan to monitor raltegravir in the post-licensure environment. Finally, I will conclude with a summary of the key

points.

[Slide 74]

As has been discussed earlier today, the doses of raltegravir studied in the phase 2 dose-ranging studies are likely on the plateau of the dose-response curve. Specifically, raltegravir doses over the range of 100-600 mg twice daily in combination regimens could not be differentiated on the basis of safety or efficacy. In addition, extensive pharmacokinetic/pharmacodynamic analyses undertaken in the context of the Phase 2 and the Phase 3 studies have not identified a relationship between raltegravir pharmacokinetics and treatment outcome.

The Phase 3 studies confirm the efficacy and safety profile of raltegravir 400 mg administered twice daily. This dose was selected because it was anticipated to provide a margin of safety and of efficacy when raltegravir was co-administered with other drugs. A key question, therefore, is did we achieve this goal? Over this and the next seven slides I will discuss the

drug-drug interaction studies that were undertaken to inform on this issue.

In evaluating the clinical significance of any changes in raltegravir pharmacokinetic parameters, upper and lower bounds were established based on clinical experience to provide guidance on making a decision about the need for dose adjustment. In the absence of a known pharmacokinetic parameter associated with efficacy, the trough concentration was chosen as a conservative parameter associated with efficacy. Based on clinical experience from the Phase 2 dose-ranging studies, a reduction in trough concentration by as much as 60 percent would not require a dose adjustment.

Raltegravir has been generally well tolerated at all doses evaluated, including in the presence of inhibitors of UGT1A1. In the absence of a known pharmacokinetic parameter associated with toxicity, the systemic exposure as measured by AUC was chosen as the parameter most likely to be associated with safety. Based on the clinical

experience of patients receiving 600 mg of raltegravir in the presence of atazanavir or tenofovir an increase in systemic exposure by as much as 100 percent would not require a dosage adjustment. With these bounds in mind, let=s now discuss the results of the drug-drug interaction studies.

[Slide 75]

Based on its routes of metabolism and excretion, raltegravir has limited propensity for being involved in drug-drug interactions either as a victim or as a perpetrator. The major route of raltegravir clearance is by metabolism by glucuronidation in the liver utilizing the UGT1A1 isoform. Raltegravir is not a substrate, an inhibitor nor an inducer of cytochrome P450 enzymes, making drug-drug interactions on this basis unlikely.

In order to assess drug-drug interactions, Phase 1 studies were undertaken in healthy subjects that evaluated the impact of co-administration of inhibitors of UGT1A1 or of inducers of drug

metabolizing enzymes, including UGT1A1, on raltegravir pharmacokinetics. In this manner it is possible to break up the impact of likely effects on raltegravir levels by other agents.

[Slide 76]

In this table results of key drug-drug interaction studies are shown by the impact of various drugs on the raltegravir pharmacokinetic parameters of C_{12} viral trough, area under the curve and peak concentration.

[Slide 77]

Looking first at inhibitors of UGT1A1, atazanavir, an HIV protease inhibitor, is an inhibitor of UGT1A1. As one would anticipate, co-administration with ritonavir-boosted atazanavir increases raltegravir levels but the effect is modest at most. Furthermore, as Dr. Nguyen noted earlier, raltegravir when co-administered with atazanavir-containing regimens is generally well tolerated. Overall, these data support co-administration of raltegravir with UGT1A1 inhibitors without dosage adjustment.

[Slide 78]

Now with respect to drugs that induce drug metabolizing enzymes including UGT1A1, rifampin is a potent inducer of drug metabolizing enzymes and was evaluated in a probe study since it likely represents the maximum effect.

[Slide 79]

As you can see, there were modest increases in raltegravir exposure and trough when co-administered with rifampin. Antiretroviral agents that are known to induce drug metabolizing enzymes include ritonavir-boosted tipranavir, efavirenz and ritonavir. Except for tipranavir, the impact on raltegravir levels was mild to modest at most. Tipranavir reduced raltegravir levels the greatest of the three drugs, with the most significant effect on trough but the magnitude of the effect was less than that which was observed with rifampin. In light of these findings, the efficacy of raltegravir in combination with tipranavir in the Phase 3 studies was carefully evaluated.

As was shown in the background document, raltegravir administered at the standard dose of 400 mg twice daily was as efficacious in regimens containing tipranavir as in those that did not. Overall, these data support co-administration of raltegravir and ritonavir-boosted tipranavir without raltegravir dose adjustment. Furthermore, they support the 400 mg dose in combination with other drugs such as efavirenz and ritonavir which have less impact on raltegravir pharmacokinetic parameters.

[Slide 80]

Finally, we evaluated the potential for tenofovir to impact raltegravir levels. Tenofovir, a nucleotide reverse transcriptase inhibitor, has been noted previously to be associated with unanticipated drug-drug interactions. Tenofovir resulted in a modest increase in exposure. The data from the clinical studies, including the Phase 2 study in treatment-naive patients, indicate that raltegravir in combination with tenofovir is generally well tolerated.

[Slide 81]

Since raltegravir has a limited potential to impact the levels of co-administered drugs, only limited studies were undertaken that evaluated the levels of other drugs co-administered with raltegravir. A probe study to evaluate the potential for cytochrome P450 3A4 mediated interactions was undertaken using midazolam, and demonstrated that raltegravir was neither an inhibitor nor an inducer of cytochrome P450 3A4, confirming the prediction based on in vitro assessment. When co-administered with tenofovir there was a mild reduction of tenofovir peak concentration with minimal effect on exposure and trough concentrations. The magnitude of these changes is similar to the reported effect of rifampin on tenofovir and there is no dose adjustment recommended for tenofovir in the presence of rifampin. In conjunction with the excellent efficacy of raltegravir in combination with tenofovir and lamivudine demonstrated in the Phase 2 treatment-naive study, these data indicate

the effect of raltegravir on tenofovir is not clinically relevant.

[Slide 82]

The Phase 2 and Phase 3 clinical data, in conjunction with the drug-drug interaction data, support the proposed dosing statement: The recommended dosage of raltegravir is 400 mg administered orally, twice daily with or without food. On the basis of the clinical safety profile in the presence of atazanavir and/or tenofovir, drugs that increase raltegravir exposure, and the efficacy in the presence of ritonavir-boosted tipranavir there is no need for raltegravir dose adjustment in combination with other antiretroviral agents.

Risk Management Plan

[Slide 83]

I would now like to provide a summary of the risk management plan proposed to monitor raltegravir in the post-licensure environment.

[Slide 84]

A detailed review of the raltegravir

development program was undertaken to identify potential risks or areas of missing information. Five items were identified.

[Slide 85]

Additional safety data, including follow up for malignancies is warranted and will be collected through a variety of mechanisms including pharmacovigilance activities, follow up in ongoing and future clinical studies and, in addition, an active post-licensure safety surveillance study is proposed. Additional details on the ongoing and future studies and the active surveillance study will be discussed in this and the next seven slides.

[Slide 86]

Immune reconstitution syndrome is a syndrom associated with potent, highly active antiretroviral regimens. Some patients experience a transient clinical deterioration following initiation of such therapy that is believed to be a consequence of the restorability to mount an inflammatory response. There were three reports of

this syndrome as adverse experiences in patients receiving raltegravir-based therapy in the clinical program. Monitoring will be provided by pharmacovigilance activities and by follow up in ongoing and future clinical studies.

[Slide 87]

Similarly, development of drug resistance will be monitored by pharmacovigilance and in future and ongoing studies.

[Slide 88]

Finally, there are no adequate and well-controlled studies in pregnant women. Therefore, the safety of raltegravir in pregnant women is not known. Raltegravir is not recommended for use in pregnancy. It is probable, however, that pregnant women will be exposed to raltegravir. Merck has already a supporter of the antiretroviral pregnancy registry and this will be utilized to follow outcomes of pregnancy exposures. Overall, we have proposed a comprehensive risk management plan to monitor raltegravir in the post-licensure environment.

[Slide 89]

At the time of the submission of the new drug application there were approximately 620 patient-years of exposure to raltegravir at any of the study doses. Over fourfold greater person-years of raltegravir exposure is planned to be collected in planned or ongoing comparative studies. Ongoing comparative studies in adult patients will provide an additional approximately 2,600 patient-years of exposure data. Protocols 5, 18 and 19 are the ongoing studies in treatment-experienced adults. Protocols 4 and 21 are the ongoing studies in treatment-naive adults, and protocols 32 and 33 are ongoing studies in stable patients, well controlled on a Kaletra-based regimen to evaluate the ability to switch patients from Kaletra to raltegravir.

[Slide 90]

In addition, additional safety data will be collected from the expanded access environment and from the pediatric program. These studies, however, do not have a comparator arm and, thus,

all the data will represent use in raltegravir-treated subjects.

[Slide 91]

An active post-licensure safety surveillance study represents a cornerstone of the proposed risk management activities. The aim of this study will be to monitor the general safety of raltegravir in worldwide usage in the post-licensure environment, including surveillance for malignancies. The incidence of medical conditions of interest in subjects treated with raltegravir will be assessed post-licensure. In order to establish an appropriate comparison two approaches will be undertaken. First, the background incidence rates of these clinical events will be established in a pre-licensure historical cohort, based on HIV patients who would have been eligible to receive raltegravir had it been available. Second, a concurrent cohort of patients not receiving raltegravir will be evaluated in the post-licensure environment. This will allow post-licensure for comparison of the raltegravir

cohort with both the historical and the concurrent control.

[Slide 92]

Let=s drill down a little bit deeper into the proposed surveillance plan. The key design elements are outlined. In this observational, prospective surveillance study we will utilize large linked medical databases to monitor the use of raltegravir in HIV-infected patients. General safety outcomes, including malignancies, resulting in healthcare utilization will be monitored every six months utilizing all exposure time after a raltegravir prescription.

An independent safety monitoring committee will oversee the study. We have proposed that this study will run for at least three years post launch. In conjunction with pharmacovigilance activities and the ongoing and future clinical studies, this active surveillance study will provide comprehensive follow up of raltegravir in the post-licensure environment.

Conclusions

[Slide 93]

In conclusion--

[Slide 94]

B-raltegravir provides a significant new treatment option for treatment-experienced HIV-infected patients. It is the first in-class HIV integrase inhibitor. It has no cross-resistance with currently licensed antiretroviral agents and is active against multi-drug resistant HIV.

Raltegravir is given one tablet twice a day without regard to food, and requires no dose adjustment when given with other antiretroviral agents. This low pill burden and convenience should support patient compliance.

The data presented today indicated it has a favorable benefit/risk assessment. Raltegravir has demonstrated rapid, potent and sustained antiretroviral activity in treatment-experienced patients. This efficacy is maximized when raltegravir is given in combination with other potent active agents. Importantly, using

raltegravir in combination regimens with other potent antiretroviral agents will enable heavily treatment-experienced patients with triple-class resistant virus to achieve undetectable HIV viral loads.

The safety profile demonstrated today is excellent based on available data, but additional follow up is warranted. A comprehensive risk management plan is being proposed to provide this follow up. When raltegravir is combined with at least one other potent active agent, the vast majority of patients achieve a virological response. The totality of the data, therefore, supports the proposed indication.

[Slide 95]

Raltegravir is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Thank you for your attention.

DR. PAXTON: Thank you very much, Dr.

Isaacs. I would also like to thank the representatives for having been extremely efficient. We are about half an hour ahead of ourselves in the program. So, I would like to suggest, if this is okay with Dr. Connelly, that we move forward to do the FDA presentation now and then we can do the break after that. Thanks.

FDA Presentation

Clinical Efficacy, Resistance and Clinical Safety

DR. CONNELLY: Thank you very much.

[Slide 1]

My name is Sarah Connelly and I am a member of the Division of Antiviral Products, and I appreciate the opportunity to speak to you all today about our review of raltegravir.

[Slide 2]

I will be discussing key portions of our efficacy review, discussing resistance data, presenting results of our safety review and then providing final conclusions.

[Slide 3]

[Efficacy]

[Slide 4]

I will highlight the key components of the Phase 2 and 3 treatment-experienced trial designs; describe demographics and baseline characteristics; present results from our week-16 and week-24 efficacy analyses; and then results from notable subgroup analyses listed on this slide.

[Slide 5]

This is similar to that previously presented, describing the two pivotal Phase 3 trial designs, protocols 18 and 19, in which the 400 mg twice daily dose of raltegravir was compared to placebo, each in combination with an optimized background therapy regimen. These two trials were identical in design, with the exception of different geographic locations. Subjects were treatment-experienced, with viral loads greater than 1,000 and resistant to one or more drugs from the NNRTI, NRTI and protease inhibitor classes. Randomized was 2:1 and the primary efficacy endpoint was a week-16 percentage of subjects with viral load less than 400. Those experiencing

virologic failure at week 16 or beyond had the option to enter open-label with a re-optimized background therapy.

[Slide 6]

Protocol 5 was a Phase 2 dose-finding study in treatment-experienced subjects where the 200, 400 and 600 twice daily raltegravir doses where compared with placebo, again, each in combination with an optimized background regimen. Subjects were included if they had a viral load greater than 5,000, CD4 cell counts greater than 50 and, again, resistance to at least one of the three classes listed. Subjects were double-blinded for at least 24 weeks during protocol 5.

[Slide 7]

The next three tables present demographics and baseline characteristics for the Phase 3 studies, and are similar to the slides presented just now by the applicant. I want to point out that between 10 and 15 percent of enrolled subjects were female. Less than 10 percent were black and less than 5 percent were Hispanic in protocol 18,

and 20 percent were black and between 15 and 20 percent were Hispanic in protocol 19.

[Slide 8]

I want to emphasize that subjects were advanced and highly treatment-experienced, with a median of ten years of prior antiretroviral therapy. Approximately one-third had CD4 cell counts at baseline of less than or equal to 50, and one-third of subjects had viral loads of greater than 100,000. In protocol 18, 20 percent of subjects were co-infected with hepatitis, and in protocol 18 approximately 10 percent of subjects were con-infected.

[Slide 9]

This table further characterizes the highly treatment-experienced nature of the study population, with 50 percent of subjects having less than or equal to one active agent in their background regimen determined by the phenotypic sensitivity score and 60 percent having a genotypic sensitivity score of less than or equal to 1.

[Slide 10]

This is the data from our week-16 efficacy analysis for the Phase 3 studies. Over 75 percent of raltegravir-treated subjects achieved a viral load of less than 400 at week 16 versus 40 percent in placebo, and this was highly statistically significant for each of the two protocols. In addition, over 60 percent of raltegravir-treated subjects achieved viral loads of less than 50 compared with 35 percent in placebo, and the increase in CD4 cell count in raltegravir-treated subjects was over twice that of those treated with placebo.

[Slide 11]

This table contains the result of our week-24 analysis. I want to draw attention to the fact that only approximately 60 percent of subjects had reached week-24 at the time of the NDA submission. That said, the 24-week analysis supports the week-16 findings and these efficacy findings are highlighted in blue. Fifteen percent of raltegravir-treated subjects experienced virologic failure, with the majority due to

rebound. Fifty percent of placebo-treated subjects experienced virologic failure, and the majority of placebo-treated subjects had failure due to non response at week 16.

[Slide 12]

The final two efficacy slides present results from selected subgroup analyses using the virologic criteria of less than 50 copies at week 16. Forty-six percent of raltegravir-treated subjects, without any active agent in their background regimen determined by PSS, achieved viral load of less than 50 copies compared with less than 5 percent in placebo. As the number of active agents in the background regimen increased, as anticipated, the treatment effect between the two groups decreased. Fifty percent of raltegravir-treated subjects, without an active protease inhibitor in the background regimen, also achieved viral loads of less than 50 copies versus 15 percent in placebo.

[Slide 13]

Naive use of darunavir and enfuvirtide was

examined. Sixty percent of subjects in the raltegravir-treated arms, without use of either active agent, achieved viral loads of less than 50 copies at week 16 versus 20 percent in placebo. Reflecting the phenotypic sensitivity score data, the treatment effect between the raltegravir and placebo groups decreased when initial use of both enfuvirtide and darunavir was used. However, 87 percent of raltegravir-treated subjects in this group achieved a viral load of less than 50 copies.

[Slide 14]

Raltegravir in combination with an optimized background regimen displayed significantly greater antiviral activity compared with an optimized background regimen alone in treatment-experienced subjects, with a statistically significant difference in week 16 viral load of less than 400 copies in two Phase 3 studies. Raltegravir=s superior antiviral activity is supported by the results from analyses of week-16 viral load less than 50 copies; change in CD4 count from baseline; the further week-24 data

and subgroup analyses.

[Slide 15]

Next I will be discussing resistance data.

[Slide 16]

Paired sequence analysis of baseline and on-treatment samples from 77 subjects with evidence of virologic failure were analyzed from protocols 5, 18 and 19, and 97 percent of the samples had genotypic mutations in the HIV-1 integrase coding region.

Three key mutations were identified, those at the 148 and 155 positions previously described by the applicant and, in addition, a third mutation was identified at the 143 position. These mutations were observed in the majority of samples and detected as early as day 27. These mutations decrease the susceptibility in cell culture, with the 148 mutation decreasing susceptibility between 24- and 46-fold and the 155 mutation decreasing susceptibility 13-fold.

[Slide 17]

Each of the key mutations was usually

accompanied by at least one additional mutation, listed on the slide. The double mutation at the 140 and 148 mutation was the most frequently detected in 35 percent of samples and increased resistance over 200-fold. The double mutation at the 92 and 155 positions was detected in 9 percent of samples and increased resistance 64-fold.

[Slide 16]

[Safety review]

[Slide 17]

I will be presenting the results from our safety analyses on mortality, discontinuations due to adverse events, serious and common adverse events, and then focused analyses of selected adverse events of interest. For several of the analyses I will be discussing data obtained from the safety update report. The safety update report was submitted to the agency two months after the initial NDA and includes two months of additional safety data, through February, 2007. I chose to use this data for key analyses in order to capture the most recent safety profile of raltegravir given

the limited duration of exposure in the current ongoing Phase 3 studies.

[Slide 20]

For the mortality analysis I examined all raltegravir doses in the Phase 2 and 3 studies using the safety update report data. There were 12 deaths that occurred during the double-blind phase-Bexcuse me, 16 deaths occurred through the safety update report, with 12 occurring during the double-blind phase. No deaths occurred in treatment-naive subjects. Therefore, further analyses are in the treatment-experienced protocols. In the raltegravir group there were 13 deaths, or 2.2 percent, and in the placebo group there were 3 deaths, or 1.1 percent.

[Slide 21]

This table lists the causes of death in the treatment-experienced studies. The majority of deaths were due to infection, highlighted in blue, and/or malignancy, highlighted in red. No deaths were considered possibly related to raltegravir by the investigator.

[Slide 22]

An analysis of baseline characteristics demonstrated that subjects who died were more advanced at baseline, as evidenced by higher baseline viral load, a lower baseline CD4 cell count, and a lower last CD4 cell count compared with surviving subjects.

[Slide 23]

Week-24 mortality is presented in the upper table. A total of 11 deaths occurred by week 24, with 8 in the raltegravir arm and 3 in placebo. Due to the 3:1 and 2:1 randomization in the Phase 2 and 3 protocols, there was greater raltegravir exposure compared to placebo and after adjustment for exposure mortality rates were 2.8 in the raltegravir group versus 2.5 in placebo.

The second table contains week-24 mortality data from other clinical trials enrolling HIV treatment-experienced subjects, specifically enfuvirtide, tipranavir and darunavir. The mortality rates in the active arms ranged between 2.6 and 4.5. We understand the limits of

cross-study comparisons, however, this comparative data provides a framework in which to put the mortality rates from raltegravir trials into context.

[Slide 24]

Mortality rates and causes of death appear similar to those observed in clinical trials enrolling similar study populations. All deaths were considered unrelated to study drug by the investigator, and our review of these cases supports the investigator assessment.

[Slide 25]

Overall there were few study discontinuations in the Phase 2 and 3 trials during the double-blind phase. Again, I used the safety update report data to capture the most recent safety profile given the limited duration of exposure. I would just like to highlight that in protocol 4, the naive study, the comparator was efavirenz and in protocols 5, 18 and 19 in the treatment-experienced the comparator was placebo.

[Slide 26]

The individual adverse events leading to discontinuation are listed, with fatal adverse events highlighted in red and additional adverse events of potential importance highlighted in blue.

[Slide 27]

Serious adverse events occurred in 20 percent of subjects and were balanced between the two arms, with pneumonia being the most common in just over one percent. Review of the investigator-assessed drug-related serious adverse events detected 16 events in 13 subjects, half in raltegravir-treated subjects. With the exception of gastritis and herpes simplex, the remainder of the adverse events are discussed in further slides. Fourteen subjects discontinued due to serious adverse events, and each of these are listed on a prior slide, representing 1.3 percent.

[Slide 28]

Common adverse event analysis was limited to the treatment-experienced studies receiving the to-be-marketed dose of 400 mg twice daily of raltegravir compared with placebo. Common adverse

events occurred in the majority of subjects, with most being mild to moderate in intensity. The most common adverse events, occurring in at least 10 percent of subjects, were observed with similar frequency in each treatment arm and were diarrhea, injection site reactions due to enfuvirtide use, nausea and headache.

[Slide 29]

Clinical adverse events reported more frequently in raltegravir-treated subjects included fatigue, nasopharyngitis, rash and herpes zoster.

[Slide 30]

Particular adverse events were selected for further exploration given their potential clinical significance. In addition, those with concomitant use of atazanavir in the background regimen were analyzed and those with hepatitis co-infection were also examined for any unique safety signals.

[Slide 31]

At the time of the safety update report with the February, 2007 database lock, there were

21 reported malignancies and, notably, none were observed in treatment-experienced subjects.

[Slide 32]

The applicant has discussed the results from the July update and we also performed an analysis using this most recent information. Thirty-six malignancies occurred in 31 subjects, with the majority occurring in the raltegravir arm. Four placebo-treated subjects experienced malignancies at the time of this July update. The distribution of subjects with malignancies is presented by protocol and dose group in the table at the bottom, with the majority occurring in raltegravir-treated subjects at the 400 mg dose.

[Slide 33]

The types of malignancies are shown here and consist of a variety of diagnoses. The time of onset in raltegravir-treated subjects was varied and there was no pattern to the numbers or types of malignancies when evaluated by time of onset.

[Slide 34]

We performed an analysis using the Phase 2

and 3 studies, limited to the double-blind phase, in which there were a total of 28 malignancies, 22 in raltegravir-treated subjects. Eight of these were recurrences. The median time to onset in the raltegravir group was 98 days versus 285 days in control. And, 2.5 percent of raltegravir-treated subjects experienced at least one malignancy compared with 1.6 percent in control. Adjusted for exposure, the malignancy rates were 2.3 in the raltegravir group versus 1.9 in control.

[Slide 35]

An additional analysis, limited to the treatment-experienced protocols 5, 18 and 19, resulted in malignancy rates adjusted for exposure of 3.0 in the raltegravir group versus 2.1 in placebo. This is more similar than our earlier analysis using the safety update report data in which the difference was 3.3 in the raltegravir group versus zero in placebo.

[Slide 36]

The identified malignancies observed were not unexpected in this heavily

treatment-experienced population. There was no clear pattern to the types of malignancies observed and the initial imbalance that was detected diminished with longer-term follow up.

[Slide 37]

AIDS-defining conditions were determined by a blinded external adjudicator in the Phase 3 studies, and 32 subjects experienced 40 AIDS-defining conditions, the majority in the double-blind period. Overall, there was no increase in AIDS-defining conditions in the raltegravir arm.

[Slide 38]

Investigation of rash events is an important part of the drug review process. In completed Phase 1 studies five percent of subjects reported rash and all were mild in intensity. Discontinuations due to rash have only occurred in a not yet FDA reviewed drug-drug interaction study of raltegravir and darunavir/ritonavir. This is a two-period study where raltegravir is given alone for four days, followed by 12 days of

co-administration of darunavir with raltegravir. This was performed in healthy adults. There have been four discontinuations due to rash, one of which being a serious adverse event. Notably, all were on the second period, taking raltegravir in combination with darunavir, and all had been on this combination regimen for at least nine days at the time of rash onset.

[Slide 39]

The Phase 2 and 3 studies were examined limited to the double-blind treatment period. Seven percent in the raltegravir group experienced at least one rash compared with five percent in control. There were no study discontinuations due to rash. Four subjects did briefly interrupt therapy, including three raltegravir-treated subjects. However, all were able to resume treatment. The median time to onset in raltegravir-treated subjects was 45 days and the median time to resolution was 20 days.

[Slide 40]

There was only one severe rash noted in

the Phase 2 and 3 protocols in a raltegravir-treated subject who was also receiving abacavir, efaverenz and 3TC. Study therapy was continued and the rash resolved. Twenty-seven rashes were assessed as drug-related and there was no imbalance between the two groups using this analysis. Three of the 17 raltegravir-treated patient rashes resolved with discontinuation of a component of the background regimen, specifically abacavir, fosamprenavir and enfurvitide. During the open-label phase there was one rash that occurred 16 days after starting raltegravir with an unchanged background regimen. The rash resolved without study interruption and no further rash occurred.

[Slide 41]

Fourteen hypersensitivity events occurred in ten subjects during the double-blind periods of the Phase 2 and 3 protocols, and there was no imbalance between the two groups. There were two serious adverse events, both occurring in raltegravir-treated subjects. One resolved after

discontinuation of darunavir and the subject resumed therapy with no further hypersensitivity events. A second subject experienced multiple hypersensitivity episodes and treatment interruptions with ultimate discontinuation of darunavir, enfurvitide and trimethoprim sulfa, and was back on raltegravir as of day 180.

[Slide 43]

In summary, the majority of rash events in raltegravir-treated subjects were mild to moderate in intensity. No rash resulted in study discontinuation during the Phase 2 and 3 development program. A clear pattern of rash has not been established, and most are self-limited, and many of the rash events have been confounded by use of concomitant medications associated with rash, such as darunavir and abacavir. At this point no clear signal has emerged, however, with further data in the future this will continue to be closely monitored.

[Slide 44]

Hepatic events are also an important part

of the safety review process of a drug application. In the Phase 2 and 3 studies 19 percent of raltegravir-treated subjects experienced a hepatic event versus 14 percent of control. There was no dose-response relationship observed. There were five serious adverse hepatic events, four in raltegravir-treated subjects, one being a hepatocellular carcinoma in a subject with underlying hepatitis B, one subject with portal hypertension and varices, one subject with hepatitis in the setting of immunoconstitution syndrome and treatment for thyrotoxicosis, and one subject with elevated hepatic enzyme who was also on darunavir therapy, and this occurred in the setting of pneumonia.

A higher rate of grade 3 and 4 bilirubin levels were noted in the raltegravir-treated subjects versus control. The majority of these subjects, as previously pointed out, were receiving atazanavir as part of their background regimen and also had elevated indirect bilirubin. There were four subjects with grade 3 or 4 bilirubin not on