DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

NDA 021-814

Proposed Tradeanem Aptivus (Tipranavir)

250 Milligrams (MG) Capsules,

Boehringer Ingelheim Pharmaceuticals, Inc.

Indicated for the Treatment of Patients With HIV

Thursday, May 19, 2005

8:00 a.m.

Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

ADVISORY COMMITTEE REPRODUCTIVE HEALTH DRUGS

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Robert Grant, M.D., M.P.H., M.S.
Veronica Miller, Ph.D.
Stephen Hall, Ph.D.
Edmund Capparelli, Pharm.D.
Gene Morse, Pharm.D.

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Frank Maldarelli, M.D.

SGE Consultants (non-voting)

Princy Kumar, M.D.

P A R T I C I P A N T S (Continued)

SGE Patient Representative (non-voting)

Linda Dee, J.D.

FDA Participants at the Table (non-voting)

Mark J. Goldberger, M.D., M.P.H.
Debra B. Birnkrant, M.D.
Rosemary Johann-Liang, M.D.
Andrea James, M.D.

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. ENGLUND: Good morning, everyone. I'm Janet Englund, and I am acting as chairperson of the Antiviral Drugs Advisory Committee today, May 19, 2005.

With this, I'd like to call the meeting to order.

I have a few opening comments that I'd like to request everyone. The first announcement--very important: in order to allow everyone to pay close attention to this important topic, we ask that everyone in the room please turn off your cell phones and pages and blackberries, and participants at the table refrain from using their blackberries and other electronic devices during this meeting. You can step outside if you need to use them. Thank you.

Introduction of Committee

At this time, I'd also like to introduce, and have our committee introduced to one another ourselves. We're going to go around the table.

What I'd first like to do is to reassure the committee that this is going to be a very interesting meeting, and that there's going to be

lots of time for questions--but, we're going to have to be doing this in a pretty organized fashion because we have a lot of material to cover today.

So I'd like to advise my fellow committee members to please keep track of your questions, because we're not going to interrupt the speakers for the questions, we're going to have designated question periods. So, for all of us on the committee, please keep track of your questions.

When you do have questions, in the question times, if you raise your hand we'll help keep track of you and everybody will get to ask their questions.

Okay--so with that, I'd like to start with an introduction. Perhaps we can start at the end of the table with Dr. Birnkrant.

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

DR. JOHANN-LIANG: Rosemary Johann-Liang,

Medical Team Leader for this product, FDA.

DR. JAMES: Andrea James, Primary Medical Reviewer for this product.

DR. HAUBRICH: Richard Haubrich, University of California, San Diego.

DR. KUMAR: Princy Kumar, Georgetown University, Washington, D.C.

DR. FISH: Douglas Fish, Albany Medical college, Albany, New York

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

DR. WOOD: Lauren Wood, National Cancer Institute, Bethesda, Maryland.

DR. DeGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

MS. PATEL: Anuja Patel, Executive Secretary for the Antiviral Drugs Advisory Committee, Advisors and Consultants Staff.

DR. RODRIGUEZ-TORRES: Maribel Rodriguez-Torres, Fundacion de Investigacion de Diego, San Juan, Puerto Rico.

DR. MUNK: Robert Munk, AIDS InfoNet.

DR. SHERMAN: Ken Sherman, University of Cincinnati.

DR. GERBER: John Gerber, University of Colorado Health Sciences Center.

DR. WASHBURN: Ron Washburn, Shreveport VA Medical Center.

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

DR. MILLER: Veronica Miller from the George Washington University in Washington, D.C.

DR. MALDERELLI: Frank Maldarelli, from the National Cancer Institute.

DR. MORSE: Gene Morse, University of Buffalo.

DR. CAPPARELLI: Edmund Capparelli, University of California, San Diego.

DR. HALL: Steve Hall, Indiana University School of Medicine.

DR. ENGLUND: Thank you, and welcome, everyone. Thank you for coming.

I should say I'm Janet Englund from the

University of Washington.

The Antiviral Drugs Advisory Committee today will discuss new drug application NDA 021-814,
Proposed tradename Aptivus--or tipranavir, at 250 milligram capsules, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.,indicated for the treatment of patients with HIV.

At this time, I'd like to remind everyone speaking that we need to speak directly into the microphone. This is being transcribed. Make sure you push the button down to talk, and make sure you un-push the button when are you are done talking.

I'd like now to have a conflict of interest statement read to us by Anuja Patel.

Conflict of Interest Statement

MS. PATEL: Good morning. The following announcement addresses the issue of conflict of interest, and is made a 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 interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions.

In accordance with 18 USC 208(b)(3), full waivers have been granted to the following participants: Dr. Ronald Washburn for ownership of stock in a competitor, worth from $50,001 to $100,000; Dr. Robert Grant, for a contract for laboratory testing with the sponsor and competitors for between $100,001 and $300,000 per year; Dr. Victor DeGruttola for his membership on an unrelated data safety monitoring committee for a parent company of a competitor, which he receives less than $10,001 per year; Dr. Edmund Capparelli has been granted waivers under 208(b)(3) and 21 USC 505(n) for a contract with competing firm for less than $100,000 per year.

In accordance with 18 U.S.C. 208(b)(3) limited waivers which allow the participants to

discuss but not to vote have been granted to the following participants: Ms. Linda Dee, for consulting for a competitor, which she receives less than $10,001 per year; Dr. Douglas Fish for lecturing for a competitor, which he received less than $5,001, for a related contract with the sponsor for less than $100,000 per year, for his employer's related contracts with the sponsor funded between $100,001 and $300,000 per year, and for his employer's contracts with a competitor for less than $100,000 per year; Dr. Princy Kumar for unrelated speakers bureau activities for the sponsor which she received from $10,001 to $50,000 per year; Dr. Richard Haubrich for a related contract with a competitor for less than $100,000 per year.

A copy of the waiver statements may 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 discussion 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 firm whose products they may wish to comment upon.

Thank you.

DR. ENGLUND: Thank you.

With that, I'd like to start the meeting by having Dr. Debra Birnkrant, the Director of the Division of Antiviral Drug Products lead us into the direction for the day.

Overview of Issues

DR. BIRNKRANT: Good morning. I'd like to welcome our Advisory Committee members and guests to this meeting. Today we will be discussing the marketing application for tipranavir for use in treatment-experienced patients with limited treatment options.

To place this application in perspective, I would like to comment on resistance in the HIV-infected population.

[Slide.]

Looking at this in a very basic way, there are different HIV-infected patient populations with drug resistant virus. There are naive subjects with acquired resistant virus, but in this group there appears to be a number of treatment options available for them.

The next group are those subjects with limited or intermediate prior treatment with HIV drugs, with resistance. And, again, in this group, it's possible to construct a viable regimen, given the limited or intermediate exposure.

However, in the last group of subjects, with extensive prior treatment with resistance, this group has extremely limited treatment options, and this is the group of subjects we'll be focusing on today.

To further put this application in perspective, I'd like to comment on HIV drug

resistance in the United States.

[Slide.]

In a study by Richman in AIDS, published in 2004, looking at the prevalence of anti-retroviral resistance in the U.S. it was shown in a cohort from the HIV Cost and Service Utilization, in those subjects with viremia, that overall resistance to anti-retroviral agents was 76 percent; 2-class resistance was seen in 48 percent; and 3-class resistance was seen in 3 percent.

[Slide.]

This slide graphically depicts the data from the article, and breaks it out by drug class.

So, with regard to the prevalence of HIV drug resistance for nucleosides, this was seen in 71 percent, whereas 41 percent had drug resistance detected to protease inhibitors, and in a non-nucleoside class, 25 percent resistance was seen.

Now as the data that generated these numbers was collected in the mid-'90s, it's possible that the prevalence rates could be either

higher or lower. They could be higher due to the extended exposure to the drugs that these patients would have seen. It could also be lower because there are more potent agents on the market after that time frame, and the practice of sequential therapy had diminished.

Nonetheless, HIV drug resistance is a problem--not only for patients, but for treating physicians.

[Slide.]

Why is it such an issue? Well, one of the main reasons is that the current state of therapy for patients with limited treatment options is in and of itself quite limited. We have Enfuvirtide--or T-20, a fusion inhibitor that's an injectable product that received traditional approval in 2004.

Now, there are a number of drugs in the antiviral pipeline, but they're in much earlier phases of development.

And now we have tipranavir, which we will be hearing about today, that was studied in two key

studies in a highly treatment-experienced population.

[Slide.]

tipranavir is a sulfonamide-containing, nonpeptidic protease inhibitors. It was studied in two key trials in this application: RESIST 1 and RESIST 2.

[Slide.]

RESIST 1 and RESIST 2 were conducted in various geographic areas--namely the United States, Canada, Europe, Latin America and Australia.

Both studies were open label, and compared boosted tipranavir plus an optimized background to a comparator protease inhibitors that was also boosted with ritonavir plus an optimized background regimen.

Dr. Rafia Bhore, in a later presentation this morning, will discuss the biases associated with open label trial designs.

Now, both protocols were amended to allow patients with protease inhibitors resistant virus to receive a PI-based regiment. This led to the

analysis of the trials as superiority trials. And, again, we will comment on this later this morning.

As with other trials that are designed to study patients with limited treatment options, these trials also had escape clauses early on to allow subjects with virologic failure to receive boosted tipranavir in a rollover study. This led to, however, a loss of the control arm at week eight. And we will be discussing this issue later today, as well.

[Slide.]

Let's look at the patient population in the RESIST trials.

They were highly treatment-experienced. They were triple-class experienced, and had a median number of 12 prior antiretroviral drugs. Prior T-20 use was seen in approximately 12 percent of subjects. Baseline resistance was high: 97 percent of isolates were resistant to at least one protease inhibitors; 95 percent of isolates were resistant to at least one nucleoside; and 75 percent of isolates were resistant to at least 1

non-nucleoside reverse transcriptase inhibitor.

[Slide.]

So, with regard to the FDA's presentation today, we will be presenting our efficacy evaluation--and Dr. Bhore will address this--and will comment on the issues that I briefly mentioned, namely: issues related to the open-label trial design, the clause to our patients to rollover to a study to be able to receive the investigational agent early on if they were failing virologically--etcetera.

This will be followed by a discussion of resistance, by Dr. Lisa Naeger who will comment on baseline genotype and phenotype and outcome, as well as the development of tipranavir-resistance in the trials, and mention cross-resistance issues.

Dr. Jenny Zheng will discuss exposure-response data, and this will lay the groundwork for the discussion later this afternoon on therapeutic drug monitoring in general, and specifically related to this product.

Dr. Derek Zhang will present drug

interactions, and will comment on the possibly complex interactions in vivo that make it difficult to predict drug interactions in general with this drug--given that it's both a CYP 3A inhibitor, as well as a P-gp inducer.

DR. Andrea James will summarize the FDA's presentation, after presenting a safety evaluation of tipranavir highlighting hepatotoxicity, rash and hyperlipidemia.

[Slide.]

At this point I would like to commend Boehringer Ingelheim for developing and studying tipranavir for use in patients with limited treatment options, and I would also like to commend the FDA review team, specifically our reviewers in the Division of Antiviral Drug Products, as well as our colleagues in the Office of New Drug Chemistry, Office of Clinical Pharmacology and Biopharmaceutics, and Office of Biometrics. Thank you.

I'd also like to reiterate what Janet said in the beginning of the meeting, in that we have a

lot of information to discuss today. And as you can see in the agenda, clarifying questions will be held after both presentations are made.

Thank you very much.

DR. ENGLUND: Thank you very much.

And, with that, I think we can begin our presentation by Boehringer Ingelheim Pharmaceuticals.

This is Dr. Burkhard Blank, Senior Vice President of Medicine of Boehringer Ingelheim Pharmaceuticals.

Sponsor Presentations

Boehringer Ingelheim Pharmaceuticals Inc.

Introduction

DR. BLANK: Good morning, Dr. Englund, Committee Members, participants of the FDA.

As you heard, my name is Burkhard Blank and, on behalf of Boehringer Ingelheim, I want to thank you for the opportunity to discuss today the NDA that was submitted for Aptivus--for tipranavir--in December of last year, with a request for accelerated approval.

[Technical difficulty, sound system.]

DR. BLANK: I must say I was not prepared this morning to trade the chair with Dr. Englund--

[Laughter.]

--but I appreciate this resolution. I think it's the best we can do.

In case you haven't heard it, my name is Burkhard Blank, and I want to thank Dr. Englund and the Committee for the opportunity, on behalf of Boehringer Ingelheim to present the NDA of Aptivus--tipranavir--that was submitted in December last year, and for which we requested accelerated approval.

Next slide, please.

[Slide.]

It has been a decade since the introduction of HIV [XXX??? sounds like HEART therapy??] therapy into clinical practice. Despite the major improvements in the life span and the quality of life for HIV-positive patients, we all know--and Debbie Birnkrant alluded to that in her introduction--that there is a growing population of

treatment-experienced patients who have limited treatment options left to them, due to the development of multidrug resistant virus.

This now includes 3 to 5 percent of newly HIV-infected patients who have transmitted multidrug resistant virus without having received antiviral treatment.

Recent studies have confirmed that treatment-experienced patients with a multidrug resistant virus have increase rates of AIDS progression and death. It is evident that there is a clear need for new treatment options for patients with drug-resistant virus.

Next slide, please.

[Slide.]

tipranavir is a novel nonpeptidic HIV protease inhibitor with potent in vitro activity against both wild type and the majority of PI-resistant HIV-1 mutants.

Because of this profile, we have developed tipranavir to address the clinical needs that I just mentioned.

The majority of the data that we will present today comes from two pivotal Phase III trails the so-called "RESIST Trials."

In these studies, tipranavir was compared with the best available protease inhibitors in patients who are highly treatment-experienced, and who have been failing the current PI-containing regimens.

When planning the clinical program, we included critical advice from experienced HIV treatment providers, from regulatory authorities--such as the FDA, of course--and from the patient community. To provide optimal care for the heterogeneous patient population that we studied in the RESIST trials, both BI and the FDA were presented with a number of trial design challenges, and also challenges when analyzing the data. Dr. Birnkrant has already addressed that in her introduction, and my colleagues will further outline this during Boehringer Ingelheim's presentation.

tipranavir clearly fulfills the

expectation that we had when we started the clinical development program. The data that we will present today, we believe, show clear efficacy and an acceptable safety profile in PI treatment-experienced patients. And therefore, we propose the following indication--Next slide, please.

[Slide.]

"tipranavir, co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-infected patients who are protease inhibitor treatment-experienced."

Next slide, please.

[Slide.]

Let me briefly go through the flow of our presentation.

Dr. Mayers, who is responsible for clinical virology, will give you an overview of the tipranavir development, including the Phase II dose-ranging study.

Dr. McCallister, who was in charge of the tipranavir clinical development program, will

summarize the efficacy of the Phase III trials, and the drug-drug interactions.

Dr. Corsico, the safety officer of Boehringer Ingelheim in the United States, will summarize the safety data; followed by Dr. Mayers, giving the overview of resistance data.

Dr. Kuritzkes will share with us his view on the clinical utility of tipranavir. And I'll come back with conclusions on behalf of Boehringer Ingelheim.

Next slide, please.

[Slide.]

I want to thank the following consultants for making themselves available to the committee today, and also for their input, advice, during the development of tipranavir, and also for preparation for today: Dr. Kashub, Dr. Morganroth, Dr. Kuritzkes, Dr. Shapiro, Dr. Lundgren, and Dr. Sulkowski.

Dr. Englund, is it okay if I now ask Dr. Mayers to take the chair?

DR. ENGLUND: Please.

DR. BLANK: Thank you.

DR. ENGLUND: Do you have a portable microphone on?

Tipranavir Development

DR. MAYERS: Good morning. I'm Doug Mayers, I'm the International Head for Virology Therapy Area of Boehringer Ingelheim, and I will present a few aspects of the tipranavir development program.

[Slide.]

tipranavir is a novel nonpeptidic protease inhibitors. It was developed to provide a new treatment option for PI-experienced patients.

It has potent in vitro activity against wild type HIV-1 and HIV-2; against the majority of clinical isolates and multidrug-resistant clinical HIV isolates.

tipranavir requires the co-administration of ritonavir to obtain effect drug levels for treatment of HIV in patients. And it's available as a soft-gel capsule of 250 mg.

[Slide.]

Briefly reviewing the tipranavir development program, tipranavir was initially developed by P&U, and acquired by Boehringer Ingelheim in early 2000. At that time, there were two ongoing Phase II clinical trials. And around early 2002, it became clear that a final dose had

not been obtained from those studies, and so a bridging Phase II study was conducted in 2002, and a meeting was held with the FDA--End of Phase II Meeting--in December of 2002.

At this meeting there was concurrence on the tipranavir/ritonavir dose for treatment-experienced patients, of 500 mg of tipranavir, 200 mg ritonavir twice a day, and an agreement on the original clinical trial design for the pivotal Phase III program.

This program was initiated in early 2003, and 24-week data became available in mid-2004. An accelerated approval was submitted to the FDA in December of 2004, based on 24-week data from two well controlled pivotal studies of 1,485 patients.

[Slide.]

tipranavir has had an extensive clinical development program, with 29 clinical trials; 25 of these trials have been conducted by Boehringer Ingelheim, with 11 in HIV-positive patients, and 14 PK and drug interaction studies in HIV-negative patients.

The pivotal trial program consists of two nearly identical studies call "Resist," which were begun in early 2003. As mentioned, they had 1,485

patients, were conducted at more than 270 sites in 21 countries.

There's an extensive safety data base for tipranavir, with 1,411 patients having been treated with a 500/200 mg dose of tipranavir, and 1,206 of these patients having received at least 24 weeks of therapy.

In addition to the pivotal trial data, there are ongoing fully accrued studies for pediatrics and treatment-naive adults which will supplement this data in the future.

[Slide.]

This slide demonstrates the need for

ritonavir co-administration with tipranavir. tipranavir exposure is markedly enhanced with ritonavir. As you can see in the dark blue is the curve of 500 mg of tipranavir given without ritonavir. In the light blue is the curve when you administer with 200 mg of ritonavir. And, as you can see, there is a fourfold increase in C-max, and a ninefold increase in AUC. But, most importantly, a 48-fold in C-min over the un-boosted tipranavir--which gives you drug levels that get above the dotted line, which is the 6.5 micro-molar target for activity in the clinic.

[Slide.]

Looking at the ADME data, in vitro, you can see that using human liver microsomes, there is inhibition of a number of the microsomes in the rank order of 2C9, 3A4, 2C19, 2D6, and 1A2 In the clinic, with the combination of tipranavir with ritonavir, we note that there's complete inhibition of 3A4. The interaction with the other CYPs in the clinic is not known at this time.

For absorption, tipranavir is formulated

as a self-emulsifying drug delivery system for solubility. Food improves this emulsification, and it is recommended that tipranavir be administered with food.

tipranavir induces the P-gp efflux transporter in the gut, which has some effect on drug interactions--this was mentioned earlier.

There's 99.9 percent protein binding.

tipranavir is a substrate and an inducer of P450 3A, but when taken with ritonavir, there is complete inhibition, and ritonavir is required to inhibit first-pass metabolism.

tipranavir circulates predominantly as unchanged drug in the plasma, and is excreted predominantly as unchanged drug in the urine and the feces.

tipranavir has a half-life of six hours in HIV-positive patients. It is predominantly excreted in the feces, with less than 5 percent of drug excreted in the urine.

[Slide.]

I'd like to briefly review the bridging PK

study we did in order to determine the dose for Phase III.

In this study, three doses of tipranavir were given: 500/100, 500/200, and 750/200 BID. These were studied in 216 patients who had 3-class and two PI experience. The first two weeks of the study was a functional monotherapy study, with the addition of optimized background regimen thereafter.

[Slide.]

The 500/200 dose was selected for the Phase II clinical trial program on the basis of several observations. The 500/100 dose was eliminated due to inferior efficacy in patients with drug-resistant viruses and more variable PK results--although this may be the optimal dose for naive patients and is being explored.

The 500/200 dose and 750/200 doses had similar efficacy and PK provides, but the 750/200 dose was eliminated due to higher grade 3/4 AST elevations, and higher treatment discontinuations, suggesting decreased tolerability. And therefore,

the 500/200 dose was selected for Phase III.

[Slide.]

At this point I'd like to briefly discuss the key mutations, because they had a pivotal role in our trial program.

These are any mutation in the HIV protease codons 33, 82, 84, or 90. And, initially, these mutations were seen to be either selected in vitro or in clinical samples from the Phase II programs, or it was seen in HIV isolates with significantly decreased susceptibility to tipranavir in early panels.

In the Phase II program, multiple PI mutations at these sites were seen to be associated with decreased tipranavir responses with three or more of these mutations; but also associated with broad, high level resistance to all of the other protease inhibitors, included saquinavir, indinavir, lopinavir and amprenavir. As an example of this, patients with virus with three mutations at these positions had a hundredfold decreased susceptibility to lopinavir.

On the basis of these observations, patients with two or less of these mutations were included in the pivotal program, whereas patients

who had three or more of these mutations were felt unlikely to get durable response to any single PI-based regiment, and were offered dual-boosted PI program--the companion study. This was a safety and PK study that was designed--the preliminary study--for a proposed third pivotal trial in patients with the highest levels of PI-resistance.

I'd like to pass the microphone to Dr. Scott McCallister, who will present the tipranavir RESIST pivotal trial program.

Efficacy and Drug-Drug Interactions

DR. McCALLISTER: Thanks, Doug.

Good morning, everyone. My name is Scott McCallister. And prior to coming to BI, I was a community HIV specialist in Chicago. But for the past five years I've been the Global Medical Leader for the tipranavir development program at BI.

I'll be going through the efficacy data from our Phase III RESIST program today, as well as

the drug-drug interaction data after that.

Next slide, please.

[Slide.]

The schematic that Dr. Mayers showed shows the dose finding study on the far left. In the center, our RESIST-1 and 2 trials are highlighted in yellow. These were nearly identical trials.

RESIST-1 was conducted in North America and Australia, and had a data base of 620 patients for safety, and 620 patients for efficacy.

RESIST-2 was conducted in Europe and Latin America, and had a data base of 865 patients for safety, and 539 patients for efficacy.

RESIST-1 was designed to lock the data base once the last patient in had completed 24 weeks. RESIST-2 was designed--we locked the data base once the last patient in had achieved 16 weeks. Therefore, as you see, 539 patients had actually gotten to 24 weeks. Not all of them had done so. But we are giving the safety data on all the patients, regardless of what point they were in the trial.

The companion study that Doug alluded to was made available to patients who were more resistant than the patients participating in the

two RESIST studies.

Next slide, please.

[Slide.]

As Dr. Birnkrant pointed out, there are challenging issues to designing trials in treatment-experienced patients. This is a heterogeneous population, and they have limited treatment options.

As a result, we conducted both of the two RESIST studies as open label trials. This was because we had four treatment options in the comparator arm: lopinavir, indinavir, saquinavir and amprenavir. We certainly made as many efforts as possible to reduce the potential for bias as a result of these open label designs. For example, we had an objective, verifiable primary efficacy endpoint, and our trial teams were internally blinded to the data until the time of data base lock.

We also had this 8-week escape, which allowed patients in the comparator arms to receive tipranavir, if they were experiencing failure in those comparator arms. That was an objective, variable endpoint also. They could not actually leave the comparator arms due to subjective

criteria, such as adverse events.

This certainly reduce the amount of patients that were in the comparator arm after eight weeks, because of the incidence of virologic failure there.

On the bottom, you see the optimized background regimen. All patients not only took their protease that was boosted in both arms, but also the best combination of nucs and non-nucs that worked for them. They could draw those choices from any available nucs or non-nucs that were marketed. And enfuvirtide could also be used--whether or not they had previously taken it.

Importantly, however, all drugs must have been pre-declared prior to randomization, so that we didn't have people changing their regimen once

they recognized which arm they had randomized to.

Next slide, please.

[Slide.]

The key inclusion/exclusion criteria are shown here. For inclusion, all patients had to have three months treatment with each of the three classes of drugs. The two PI regimens had to occur for at least three months; one of those PI regimens had to be the current regiment. Treatment interruptions just prior to entering the resist studies were not permitted. Viral loads had to be 1,000 copies/ml; any CD4 count. And the baseline genotype had to have at least one of these primary mutations drawn from the IAS USA list, essentially to ensure adherence, such that patients participating in the RESIST studies were adhering to their treating and were likely to have a response in RESIST.

Exclusion criteria: patients that had more than two mutations at these key positions: 33, 82, 84, or 90, were not allowed to participate in the RESIST studies but, as Dr. Mayers stated, we

offered them the dual boosted PIs in the companion trial 1182.51. All patients had to have acceptable safety screening labs, up to DAIDS Grade 1 values, with the exception of lipids, which were permitted to be up to DAIDS Grade 2.

All patients had to have an expected survival of at least 12 months, and patients with a survival expectation of less were prohibited. We didn't have a Karnofsky score to verify this. This was in the opinion of the participating investigator.

Next slide, please.

[Slide.]

Here is the schema for screening and randomization. On the far left you see all patients had a screening genotype at baseline. They either had the true gene test by visible genetics in the RESIST 1 study, or the Virtual Phenotype test in the RESIST 2 study. However, some patients in Latin America, due to the difficulty of getting their tests all the way to Belgium, had the TruGene test performed in the

United States.

Once that data was available on the screening genotype, investigators used both the patients treatment history and the interpretation and resistance mutations from those reports, and made their selections. They selected the comparator PI and they selected the optimized background regimen "OBR."

If they needed assistance in selecting the comparator PI, they were allowed to use one of our three international resistance experts, who were essentially on call to the investigators at all times.

We then performed a randomization. The randomization was stratified on the basis of the particular comparator PI they had chosen, as well as whether or not they had pre-chosen enfuvirtide.

We did a one-to-one randomization: half the patients went into the tipranavir arm, the other half went into the comparator arm and received either lopinavir, indinavir, saquinavir or amprenavir--all ritonavir boosted.

At the same time they began these treatments, they also began that optimized background regimen.

Next slide, please.

[Slide.]

Our 24-week efficacy endpoints are shown here. On top, the primary endpoint was defined as: the treatment response which was a confirmed 1 log reduction in viral load at 24 weeks, without viral rebound, drug change, study discontinuation or death. So if, for example, a patient had a 1.0 log drop at week four, and then just a 0.5 log drop at week eight, that would not have been confirmed virologic success, and that patient might have been a virologic failure.

Secondary efficacy endpoints are shown on the bottom: change in viral load from baseline; the percentage of patients who were undetectable at a 400-copy and a 50-copy cut-off; the change from baseline CD4 count; and the number AIDS progression events.

Next slide, please.

[Slide.]

As a result of speaking with our investigators as we were preparing these trials, we determined that they were going to be difficult to enroll if we excluded patients who were resistant on their baseline genotype to all PIs. Therefore,

prior to any patient randomizations, we wrote an Amendment #2 that allowed PIs that the genotype report interpreted as pan-resistant. Our rationale was that the interpretation guidelines on the geno report had changed just prior to the study initiations of RESIST in early 2003.

Importantly, the resistance interpretation on the genotype report is not generally based on ritonavir-boosted versions of those PIs. Investigators had the genotype results, as well as expert consultation available to select the optimized drug for their individual patient. And if they needed assistance, they could use those experts, as well as other materials that we made available.

Importantly, the study would have enrolled

extremely slowly had we not implemented this important amendment.

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[Slide.]

Here are the baseline demographics.

More than 3,300 patients screened for the two trials. The 24-week efficacy data was available for 582 in the tipranavir arm, and 577 in the comparator arm.

The two arms were essentially similar across these characters: with a median age of 43; more than 85 percent of the patients were male; 71 to 74 percent of patients were White; they had a baseline viral load of over 4.8 logs; more than 155 CD4 cells at baseline across the two arms; and between 10 and 15 percent of patients had either hepatitis B or C at baseline.

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[Slide.]

These patients were very advanced, with 88 percent of them carrying an AIDS diagnosis when they began the studies. The median drug use was:

six NRTIs, 1 NNRTI and 4 PIs coming in. In fact, 45 percent of them had taken five or more PIs; 12 percent had previously taken enfuvirtide.

They had limited options to add active drugs to their background regimen. In fact 44 percent of the patients coming in had a baseline GSS of 1 or less from the drugs that they chose.

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[Slide.]

These data on phenotype were not made available to investigators at the time of choosing their pre-selected regimens. They had the genotype reports. However, we randomly selected samples--a subset of the total--here. And what this shows is the median IC 50 changes for tipranavir, as well as the other drugs that were used in the study.

As you see, for tipranavir, there was a 1.7 IC 50 change on median for 450 isolates, and very high numbers for lopinavir, indinavir, saquinavir and amprenavir--each of them above the cut-off for those drugs.

Next slide, please.

[Slide.]

The pre-selected comparator PIs are shown here. Lopinavir was the most common drug

pre-selected--by more than 50 percent of patients; amprenavir, nearly 26 percent; saquinavir, 20 percent; and indinavir, less than 4 percent.

Next slide, please.

[Slide.]

Here are the primary efficacy results: the 1-log viral load reduction from baseline confirmed.

This slide is divided up into RESIST 1 and RESIST 2, but the others that you will see that follow, I've combined the data.

The percentage of patients with a 1-log drop for the tipranavir arm: 41.5 percent in RESIST 1, 41 percent in RESIST 2. For the comparator arm: in RESIST 1, 22 percent; and 15 percent in RESIST 2.

As you see, the P values here, each of these were highly significant results.

Next slide, please.

[Slide.]

Now the two trials are combined. Overall then, 41.2 percent of patients for the two tipranavir arms achieved the 1-log viral load treatment response, and 19 percent of patients in the comparator arm--again, a highly significant difference.

Next slide, please.

[Slide.]

This is the undetectable viral load: "<400" on top, "<50" on the bottom. In the <400 figure, 34 percent of patients in the tipranavir arm, and 15 percent in the comparator arm achieved that endpoint.

In the <50 figure, 24 percent in tipranavir, and 9.4 percent in comparator--again, both of these with significant P values.

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[Slide.]

Viral load reduction is shown on top here. The absolute viral load reduction from baseline for tipranavir was .8 logs, and for comparator was .25 logs.

The CD4 count increase is shown on the bottom: for tipranavir, 34 cells, and for comparator, 4 cells. And, again, each of these results was highly significant at the 24-week endpoint.

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[Slide.]

So, in summary, primary endpoint and each of our secondary efficacy endpoints had higher

significant results between the tipranavir and comparator arm. Down on the bottom, the AIDS progression events, there was a numerical difference between the two: 25 in the tipranavir arms, and 34 in the comparator arms, but this was not a statistically significant difference.

Next slide, please.

[Slide.]

This slide shows several important concepts. Patients were allowed to use enfuvirtide coming in. If they used enfuvirtide, their median CD4 count in the tipranavir arm was 72, and the comparator arm 77, indicating a little bit more

advanced population that was choosing enfuvirtide use. Their viral loads were a bit higher than the general population in RESIST--a little over 5 logs in each of the two arms; and the number of prior antivirals used was also higher.

If they were naive to enfuvirtide coming in--had never taken it before--these data are shown on the left. tipranavir, and using enfuvirtide, they had a 69.6 percent treatment response--the 1-log viral load reduction from baseline; comparator naive to enfuvirtide and using it, 28.7. So the tipranavir arm improved from 41 to 69; the comparator arm, from 18.9 to 29.7.

If they had used prior enfuvirtide, as you see on the right, and they took tipranavir, they had a 27.9 percent response. If they took one of the comparator arms, it was a 17.6 percent rate of response.

Next slide, please.

[Slide.]

So, in conclusion for our efficacy data from the Phase III program, tipranavir as superior

at 24 weeks to the comparator arms in our two well-controlled studies in treatment-experienced population. This occurred for the treatment response, the absolute viral load reduction from baseline, the percent undetectable, and for the CD4 cell count increase.

Next slide, please.

[Slide.]

Because tipranavir is an inducer when combined with ritonavir, there is net inhibition of the CYP 3A4 system. And, because of P-gp effects, we conducted a pretty extensive drug-drug interaction program.

Next slide, please.

[Slide.]

On top, you see the antiviral drugs that we studied. Our initial study was a screening trial where we looked at seven three-drug regimens, and added tipranavir to them; for example, somebody could be taking D4T, 3TC and naviripine. We added tipranavir, and we wanted to see what the effect was on each of those drugs. We did that for seven

common drug regimens.

We also looked at tipranavir in dual-boosted PI regimens, in the companion trial that we've alluded to, where tipranavir was combined with lopinavir, saquinavir or amprenavir. We also did individual drug-drug interaction trials in HIV-negative subjects, looking at zidovudine, ddI, tenofovir and efavirenz.

Other drugs commonly used by patients living with HIV, we looked at tipranavir with estrogen-based compounds, with loperamide, atorvastatin, clarithromycin, fluconazole, and rifabutin.

We also looked at antacids. And, as Dr. Mayers described, performed an ADME study.

Next slide, please.

[Slide.]

The notable drug interactions for RT inhibitors are shown here. There were no relevant changes in drug levels when tipranavir was combined with 3TC, D4T, tenofovir, nevirapine or efavirenz.

In the case of zidovudine, the AUC was

reduced 30 to 40 percent in the presence of tipranavir, and the tipranavir C_{min} and AUC were essentially unchanged.

Abacavir, the AUC was also reduced--about the same as for zidovudine. This trial did not allow the evaluation on tipranavir levels.

In the case of ddI, the AUC was reduced by 10 percent in the presence of tipranavir 500 and 100, which was one of the early doses we were studying before we had our final dose for Phase III. And the tipranavir C_{min} was reduced by about 34 percent; the AUC unchanged.

While, the levels of NRTIs were reduced, the actual clinical relevance of these changes is unknown, and we cannot make any recommendations at this time about dose adjustments.

Next slide, please.

[Slide.]

The companion trial was essentially a safety and PK trial that was available to patients, again, who screened for either of the two RESIST program studies.

Next slide, please.

[Slide.]

On top, you see that all patients received

a single boosted PI for weeks 0 to 2 in this trial. At week 2, tipranavir was added to each single boosted-PI arm. Then, at week 4, we tested the plasma concentrations of the other PI and compared what they were in the presence of tipranavir to what they were without tipranavir at week 2.

The data is shown in this table.

In the case of lopinavir, saquinavir and amprenavir, you see large magnitude reductions in AUC, C max and Cmin for each of the three drugs. On the basis of these data, we do not recommend the co-administration of tipranavir in dual boosted-PI regimens with these drugs.

Next slide, please.

[Slide.]

So, in conclusion from our drug-drug interaction program, there were no relevant changes in drug levels for 3TC, D4T, tenofovir, naviripine or efavirenz.

In the case of lopinavir, there was no relevant change in drug levels, because lopinavir essentially acts locally.

Drug level reductions of uncertain clinical relevance, where a dose adjustment cannot be recommended at this time occurred in the case of

zidovudine, abacavir and ddI.

As you just saw in the last slide, there were significant drug level reductions for lopinavir, saquinavir and amprenavir. And, as I mentioned, these combinations are not recommended.

Clinical monitoring is advised, and an alternative agent should be used, if available, in the case of these other drugs. For atorvastatin, we saw and eight- to 10-fold increase in atorvastatin levels--similar to what's been described where atorvastatin is combined with other PIs, but nonetheless if a drug such as pravastatin, which doesn't go quite as much through the 3A4 system can be used, or a non-statin, such as a fibrate can be used for lipid lowering, that's what we would suggest.

In the case of clarithromycin and fluconazole, there were a two-fold increase in tipranavir levels, so patients who need those particular drugs to treat an opportunistic infection, or prophylax for it, we suggest starting at the lower doses of those drugs, and then titrating up with careful clinical monitoring, as needed.

In the case of ethinyl estradiol, as has

been described for other PIs, there was a large magnitude--50 percent--reduction for estrogen. So women needing ethinyl estradiol for oral contraceptive should be aware they need a barrier contraceptive. Women using for hormone replacement should make sure they have clinical monitoring of their hormone status.

For rifabutin, similar also to what's been described for other PIs, we suggest a reduction of the dose to 150 mg three times a week. That's because rifabutin levels were increased by about three-fold, and rifabutin metabolite levels, about 20-fold.

Next slide, please.

[Slide.]

This slide shows drug interactions that we have not performed, but on a hypothetical basis, we have some recommendations.

Potential drug level increases may occur for the azoles, for the erectile dysfunction drugs, and for desipramine. Potential drug level decreases may occur for methadone, for buprenorphine or for meperidine. And there are unpredictable interactions in the case of warfarin, theophylline, serotonin re-uptake inhibitors,

calcium channel blockers, immunosuppressants, anti-psychotics and oral hypoglycemics. Therefore, we recommend clinical monitoring for each of these. When laboratory testing is available, obviously we would suggest that as well.

Due to the alcohol that is contained in the tipranavir capsule, we suggest that patients who are taking disulfiram, or disulfiram-like metronidazole, be aware of the potential for disulfiram reaction.

Next slide, please.

[Slide.]

Thanks for your attention. I'd like to now turn it over to my colleague Dr. Chris Corsico from Safety.

Safety

DR. CORSICO: Thank you, Scott. Good morning, Dr. Englund, members of the Committee.

My name is Chris Corsico. I'm the Head of Drug Surveillance and Information for Boehringer in the United States. And it's my pleasure to present to you the safety profile of tipranavir that emerged during our clinical development program.

Next slide, please.

[Slide.]

The safety data base actually consists of over 3,000 HIV-positive treated patients. As you may note that this data base is larger than the efficacy data base for two reasons. First, we cut the safety data base beyond the 24-week cut for the efficacy analyses to provide you with the most current safety analyses that we submitted to the

agency. The second reason is: the safety data base contains any patient who was exposed to at least one dose of tipranavir.

There were over 1,400 HIV-positive patients at the to-be-marketed dose of tipranavir, 500mg/200mg. And that represents approximately 1,200 patient-years of exposure. About half of that exposure actually comes from out RESIST program--the 748 patients randomized to receive tipranavir. As a result, for the remainder of the safety talk, I will focus on the safety findings from the pooled RESIST analyses.

Next slide, please.

[Slide.]

This slide presents for you the patients remaining on study during the course of the RESIST program. Along the y-axis, we have numbers of patients, and along the x-axis we have weeks in study.

What you can see is that for the first eight weeks of the study, the two arms track closely. However, after week eight there's

differential drop-out. As noted earlier Dr. Birnkrant and then by Dr. McCallister during his Efficacy presentation, there was an escape clause in the RESIST program that allowed patients who were failing their comparator PI at week eight to leave the comparator and rollover to our long-term follow-up study where they could receive tipranavir. As a result, after week eight there's a tremendous differential dropout. The differential dropout results in a difference of exposure of 615 patient-years for our tipranavir-treated patients, versus 406 patient-years in the comparator treated patients--or 50 percent more patient years of exposure in the tipranavir-treated patients.

As you can see down here, the main reason for that differential dropout is lack of efficacy in the comparator arm.

Next slide, please.

[Slide.]

The next two slides provide for you the common adverse events reported in greater than 5

percent of patients exposed to tipranavir and comparator in our RESIST program. And what you see are two patterns.

The first is: gastrointestinal side effects were the most commonly reported side effects during the RESIST program. This wasn't a surprise, because gastrointestinal side effects have been reported with other ritonavir-boosted protease inhibitors.

In addition, "infections" was the next largest group of adverse events reported, followed by fatigue and pyrexia in this general category. This represents the underlying patient population treated with tipranavir: antiviral-resistant, highly treatment-experienced patients.

The next slide summarizes the remaining common adverse events that were found in the RESIST program.

[Slide.]

During the course of our Phase I and Phase II, three safety signals emerged that required further investigation: rash, hepatic events and

hypertriglyceridemia and hypercholesterolemia.

What I'd like to do is spend a little bit of time talking about each of these three areas.

[Slide.]

As you can see here from our RESIST experience, the incidence of rash in the tipranavir-treated patients, unadjusted, was slightly higher than that for the comparator arm. However, during our Phase I program, there was a signal that healthy women exposed to tipranavir developed rash, and that incidence of rash was actually further increased when women were also given ethinyl estradiol.

In order to better try to understand this, we looked to our RESIST data set.

Next slide, please--

[Slide.]

--shows the incidence of rash in the RESIST data set broken down by gender. And we find that women have a higher frequency of reported rash, compared to men.

In order to understand what risk factors

may be contributing to this, we did a logistic regression model shown in the next slide.

[Slide.]

This model included age, gender, baseline CD4, tipranavir and ritonavir trough levels, race, hepatic co-infection and weight. The model showed significance for a low CD4 count of less than 50 when compared to CD4 count of greater than 200.

In order to better understand this, however, what we decided to do was to look at the incidence of rash, stratified by the CD4 breakdown, looking at our women patients. And that's shown on the next slide, please.

[Slide.]

And what you see is a normal distribution of rash, based on women who had a CD4 count less than 50, women with a CD4 count of 50 to 200, CD4 count of greater than 200 to 350, and then a CD4 count greater than 350.

We are unable to draw any definitive conclusions from this analysis. As you know, about 16 percent of the patients in the RESIST program

were women, and the numbers here are too small to draw any definitive conclusions at this time with respect to rash. However, the company is committed to further studying this and to further investigating this finding.

The next safety hypothesis--signal--that emerged from our development program was that of hepatic events. During our Phase I and Phase II program, we saw a dose response with a higher incidence of elevated liver function tests in patients receiving higher doses of tipranavir.

Next slide, please.

[Slide.]

In order to better understand this, we turned to our RESIST data set just to take a look at patients who developed an elevated Grade 3 or 4 ALT, AST or total bilirubin. For the remainder of the talk I will refer to these as "elevated liver function tests," although total bilirubin is really not a liver enzyme.

What we find is that approximately 10 percent of the tipranavir-treated, versus 3.5

percent of the comparator-treated, developed a Grade 3 or 4 elevation in their LFTs. The majority of the patients, however, who developed this Grade 3 or 4 abnormality are able to continue or temporarily interrupt their medication and continue therapy. In this group, a small number of patients developed a serious adverse event with an hepatic term: those were elevated ALT and a hyperbilirubinemia case. All these patients, again, were able to continue on their medication.

There was a smaller number of patients who actually discontinued their therapy. The majority of those patients--12 of the 17--actually had their liver function tests return to baseline or normal, and had no serious adverse event with an hepatic term reported.

There were five patients in this group who developed an SAE with an hepatic term. Four of the five patients, after discontinuing their medication, had resolution of their elevated ALT, AST or bilirubin, or returned to their previous baseline. There was one patient--hepatitis B

co-infected, with a CD4 count of less than 50 at the time of initiative tipranavir--that actually died. That patient had hepatic failure in the setting of progression of their underlying HIV disease, and their CD4 count at the time of death was also less than 50.

Next slide, please.

[Slide.]

In order to understand what potential risk factors contribute to increasing risk of Grade 3 or 4 LFTs, we did a contragression model, and actually found that based on ALT, AST or total bilirubin of Grade 1, compared to less than or equal to Grade 1; CD4 counts greater than 200, compared to those less than or equal to 200; and hepatitis B or C co-infection, increased one's risk of developing Grade 3 or 4 elevations in LFTs--on the order of around two to two-and-a-half-fold.

When the treatment was put into this model, we found that tipranavir independently increased that risk 2.4-fold, on the order of baseline LFTs and hepatitis co-infection.

Next slide, please.

[Slide.]

Based on our findings from RESIST, any

patient who starts tipranavir should have monitoring. Routine clinical and laboratory monitoring to detect abnormalities is recommended. And in patients who have chronic hepatitis B or C, elevated LFTs at initiation of tipranavir therapy, require more frequent clinical and laboratory monitoring.

Finally, any patient who is symptomatic in the setting of elevated LFTs should have their tipranavir discontinued.

The third signal that emerged during the early development program was that of hypertriglyceridemia, and hypercholesterolemia. This next slide summarizes those findings--what we found in the RESIST program.

[Slide.]

In RESIST, 23.5 percent of the tipranavir-treated patients, versus 12.3 percent of the comparator-treated patients developed a Grade 3

or 4 elevation in their triglycerides; 3.9 percent of the tipranavir-treated patients, versus .4 percent of the comparator-treated patients developed a Grade 3 or 4 elevation in their cholesterol.

Obviously, the most important thing is to understand what the potential clinical sequella are of these elevated serum lipid levels. Therefore we looked at cases of ischemic heart disease in the RESIST data set, and cases of pancreatitis, to ascertain whether or not we were seeing differentials with respect to potential long-term and acute toxicities associated with elevated plasma lipids.

With respect to ischemic heart disease, we found no significant difference in angina or myocardial ischemia between the two treatment groups. However, the duration of follow-up is too short to draw any definitive conclusions. The company is committed to further studying this so we can understand what the long-term potential sequella are of tipranavir and this

hypertriglyceridemia and hypercholesterolemia seen in these treated patients.

With respect to a potential for acute toxicity--pancreatitis--we found no difference between the two treatment arms: four cases in the tipranavir arm versus three cases in the comparator arm.

Next slide, please.

[Slide.]

Finally, we turn to the RESIST data set to look at fatal outcomes. And we've compared fatal outcomes in the tipranavir-treated arm versus the comparator-treated arm in an exposure-adjustment analysis shown here on this Kaplan-Meier curve.

And what the curve demonstrates is that there's no significant difference between fatal outcomes between the two treatment groups. This was not a surprise, however, because the studies were designed, actually, to detect the virologic endpoint, not a clinical outcome endpoint.

We should note that for both treatment groups, the majority of the events that were

reported by the investigator as cause of death were AIDS-progression events, opportunistic infections, and neoplasms, consistent with the patient population under study.

Last slide, please.

[Slide.]

In conclusion: approximately 1,200 patients have been treated with the to-be-marketed dose of tipranavir for at least 24 weeks. Treatment-experienced antiretroviral-resistant patients with infections and AIDS-progression events were the events that were commonly reported during the course of the RESIST program. The adverse event profile for tipranavir is similar to ritonavir-boosted protease inhibitors, with the exception of elevated liver function tests and clinical hepatic events, and elevated triglycerides and cholesterol.

At this point I'd like to turn the mike back over to Dr. Mayers, who will talk about resistance.

Resistance

DR. MAYERS: Thank you, Chris.

[Slide.]

Looking at the emergence of drug

mutations, we had 217 patients in Phase II; 59 patients in Phase III. For these patients, we obtained the baseline isolate, the first viral rebound isolate, and the last on-treatment isolate to look at emergence of resistance. And, again, not surprisingly, the 33 FINV, 82 TNL, and 84 V mutations are the predominant emerging mutations with tipranavir.

Of note, with the 82 wild type position, a single-base mutation to V82L is seen, and we believe this is a signature mutation for tipranavir, with V82A, which is the most common mutation in treatment-experienced patients--again, a single-base mutation produces a V82T.

At this point we don't have failure samples from our treatment-naive population to describe the pathway to resistance in drug-naive patients.

[Slide.]

Looking at what predicts the viral load response at 24 weeks, we used a multivariate regression model and, not surprisingly, tipranavir, use in enfuvirtide, available background drugs of nucs or non-nuc class, and tipranavir score all were significant in predicting the 24-week

response.

tipranavir, as well as ritonavir, was responsible for a 1-1/4 log reduction of viral load. Enfuvirtide use was associated with approximately a 1 log further reduction of viral load. Each additional nuc or non-nuc in the OBR that was genetically available was associated with 1/4 log response, and the tipranavir score permutation was associated with a reduction of .17 log response. And basically that adds up to seven or eight of the tipranavir mutations are required to eliminate the tipranavir effect, which is a good correlation with the tipranavir score that was shown previously.

[Slide.]

So, in conclusion, tipranavir has a high

genetic barrier to resistance. It takes eight of the tipranavir-specific mutations to produce high level resistance. The tipranavir mutation score, we believe, represents a unique group of protease gene mutations as the most specific marker for tipranavir resistance. And, as I mentioned earlier, about half of these mutations appear to be newly described for tipranavir.

Looking at susceptibility, we believe that less than three-fold wild type is susceptible; three to 10-fold wild type is decreased susceptibility; and greater than 10-fold wild type would be resistance.

Relating genotype to phenotype, "susceptible by genotype" would be zero to two of the key mutations, or zero to four of the tipranavir score mutations. "Possible resistance or decreased susceptibility" would be three of the key mutations, or five to seven of the tipranavir score mutations; and "resistance"--or greater than 10-fold decrease in susceptibility--requires all four of the key mutations, and eight or more of the

tipranavir score mutations. So there's a nice correlation between the genotypic scores and the phenotypic analysis.

Finally, the predominant emerging mutations with tipranavir are at positions 33, 82 and 84.

Because the Committee's been asked to address tipranavir drug levels, I've included four slides in the presentation to some of Boehringer interpretation of that data.

[Slide.]

This first slide shows the two-week viral load reduction by the drug levels with tipranavir. And we saw, both in the functional monotherapy portion of the 52 with the Phase II study, as well as in the Phase III study, that when the tipranavir drug level was greater than 6.5 micromolar was seen--which produces roughly 30-fold--an IQ of roughly 30, what you can see is once you get above that level, the patients have a 1 log two-week response, which increases somewhat as the drug levels get higher. Of note: only 4-1/4 percent of

patients have drug levels below that 6.5 micromolar cutoff.

Looking at relationship to hepatotoxicity, we also see the trend toward increasing hepatotoxicity as tipranavir levels increase, but it's a very gentle trend, from 20 to 120, and then there's a rise--a significant rise--in hepatotoxicity with levels above 120 seen in our pivotal trial program. It should be noted that 2 percent or less of patients have drug levels above 120 in our clinical trial program.

[Slide.]

But when you get to the individual patient and look at these drug levels, these are the patients who had normal ALT, AST. These are the patients with Grade 3, 4 ALT/ASTs--and the tipranavir levels. And while you can see that there's a trend, there's a dramatic overlap--a very broad range of levels in patients who have or do not have hepatotoxicity.

[Slide.]

Similarly, looking at geometric trial

concentrations of multiple tipranavir toughs versus viral load response, this shows the viral load response at 24 weeks in the patients receiving tipranavir, by drug level. And it's not clear how this data would be used to improve patient management.

[Slide.]

So, in conclusion, tipranavir trough levels greater than 6.5 micromoles was associated with 1 log response at two weeks. Only 4-1/2 percent of patients have levels less than that.

tipranavir trough levels of greater than 120 are associated with hepatic events, but 93 percent of patients have tipranavir levels between 6.5 and 120 micromolar.

There are weak trends associating tipranavir trough levels with hepatic events and treatment responses, but the large inter-patient variability will limit the utility of these measures in clinical practice.

I'd like to pass the mike to Dr. Dan Kuritzkes of Harvard Medical School, who will

discuss the clinical utility of tipranavir.

Potential Utility of Tipranavir in Current Clinical Practice

DR. KURITZKES: Thank you very much, Doug.

Having been an investigator in the original Phase I-II trials of tipranavir, it's a particular pleasure to have the opportunity to address the Committee this morning on my view of the clinical utility of this drug, and to see all the work of the last several years come to fruition.

[Slide.]

As you heard already from Dr. Birnkrant, there are a growing number of patients with highly drug-resistant HIV. The durable success of salvage therapy regimens depends on the number of active drugs available for the construction of such regimens.

Currently, there are many patients and clinicians who are holding back on the use of valuable drugs such as enfuvirtide, while awaiting the availability of other drugs with which to

combine those agents. Maintaining patients on active antiretroviral therapy clearly delays AIDS progression and AIDS-related mortality. And the more drugs we have available to do this, the better our patients will be.

[Slide.]

In this slide I've summarized several of the recent studies addressing the prevalence of drug resistance in treatment-naive and treatment-experienced populations. Clearly, the prevalence is on the rise. The HCSUS study that Dr. Birnkrant already summarized for you showed a 41 or 43 percent prevalence of PI resistance in the 1,100 viremic patients who were analyzed. We have recent from Diane Bennett at the CDC, presented at CROI a few months ago, from their surveillance efforts, showed that among treatment-naive newly-diagnosed individuals, the prevalence of drug resistance had reached over 15 percent. And, as you heard from Dr. Blank, that translated into about 3 percent of individuals who had multidrug resistance, including--notably--the New York City

patient and similar patient that we saw in Boston over the summer--who had multiple PI resistance for whom tipranavir, in fact, would have represented the only potentially active protease inhibitor, despite the patients themselves being PI-naive.

And then lastly, from a cohort in London, the CHIC study, showing a 25 percent risk of development of resistance to any drug over six years for patients initiating three-drug therapy, and an approximately 5 percent risk of developing a multiple drug resistance over the same time period.

[Slide.]

The relationship between treatment and mortality, and the mortality of patients with a history of treatment failure has been analyzed in the PLATO study, a collaboration that pooled data from 13 cohorts across Europe, North America and Australia. This retrospective evaluation of patients with triple-class failure analyzed information from over 15,000 patients, of whom nearly 2,500 had experienced virologic failure. There had been 276 deaths among those failure

patients, and it's notable that two-thirds of those deaths were attributable to an HIV-related cause.

What is of particular interest here is that the overall mortality rate was approximately five per 100 person-years, but that rate increased four-fold for subjects or patients with CD4 counts less than 50, and the relevant hazard for death was nearly three-fold higher for patients not on antiretroviral therapy. So maintaining antiretroviral therapy, even in the setting of prior treatment failure had an apparent benefit in deferring mortality.

When one looks at all the data in that study, one can conclude that maintaining virus loads below 10,000 copies per ml, and maintaining a CD4 count above 200 is associated with reductions in mortality.

[Slide.]

Well, what are the goals of antiretroviral therapy in these treatment-experienced patients? I think your goal remains the same as it is for patients who are treatment-naive, and that is: to

the complete suppression of plasma HIV RNA to levels below detection.

Now, previously, this goal had been much more difficult to achieve in this population. But now as new drugs are developed--drugs like enfuvirtide and like boosted-tipranavir--this goal again becomes an achievable one. As you saw from the summary by Dr. McCallister, both patients who were T-20-naive, and added T-20 to tipranavir, achieving nearly a 70 percent likelihood of having complete suppression by week 24.

But achieving this objective clearly requires active drugs in order to construct fully potent regiments. The broad activity of boosted-tipranavir against protease inhibitor-resistant viruses make it an important new antiretroviral drug for clinicians seeking to construct regimens for treatment-experienced patients.

[Slide.]

To summarize the efficacy of tipranavir: this drug has potent activity against PI-resistant

viruses. There was immune reconstitution commensurate with the degree with viral load decrease in the RESIST trials. This was associated with lower number of AIDS-progression events in the tipranavir arms, although this was not a statistically significant difference. And clearly, as shown in the RESIST studies and in the companion trials, the durability of the tipranavir response depends on available of other active agents in the background regimen.

[Slide.]

Let me address briefly the toxicity concerns and put them in context.

Certainly, elevation of hepatic transaminases, as you heard, emerged as an issue. We know that somewhere between 6 and 30 percent of patients receiving antiretroviral therapy are likely to develop significant elevations in their hepatic transaminases. Those risks are greater for patients who are co-infected with hepatitis B or C virus, and are most pronounced among patients receiving high dose ritonavir--a situation that is

really no longer that relevant.

In studies done by Mark Sulkowski in the Moore Clinic at Johns Hopkins, looking at nearly 1,200 protease inhibitor-naive patients who received an initial PI-containing regimen, the incidence of severe Grade 3 or 4 elevations in hepatic transaminases was around 13 percent, which is similar to the range observed in the RESIST studies.

[Slide.]

As regards elevations in serum cholesterol and triglyceride levels, certainly these increases could expose patients to an increased risk of atherosclerosis over time with longer term exposure. The magnitude of those risks is still a matter of study, and the cholesterol elevations more likely to be of concern than the triglyceride elevations in that regard.

High triglyceride elevations, in theory, could result in an increased risk of pancreatitis. But, in reality, clinical pancreatitis in subjects receiving ritonavir-boosted protease inhibitors

with increased triglyceride levels has really been an extremely rare event.

[Slide.]

Well what, then, is the role of boosted-tipranavir in treatment-experienced patients? Boosted-tipranavir has shown significant antiviral activity in patients with PI-resistant virus, resulting in virologic and immunologic superiority over the comparator protease inhibitor arms in the RESIST trials.

The increased risk rates of lipid elevation and hepatotoxicity seen in the RESIST trials in the tipranavir arms compared to the comparator arms are clear that those risks can be managed with appropriate medical and laboratory monitoring.

The use of boosted-tipranavir should be based on an assessment by clinicians of the resistance profile of the patient's virus; the risk of toxicity for the individual patient; and the availability of additional drugs with which to construct a fully potent antiretroviral regimen.

[Slide.]

In conclusion, then, to summarize my feelings on where boosted-tipranavir should and

will be used: as with any drug, boosted-tipranavir requires additional active drugs to obtain a durable response. For patients like those evaluated in the RESIST program, enfuvirtide may be the only remaining active drug with which to combine tipranavir and ritonavir.

Use of boosted-tipranavir in populations with less extensive prior treatment history, and less extensive resistance than found in the RESIST population, expands the number of active drugs available to combine with tipranavir-ritonavir, and therefore may increase the likelihood of achieving a durable response.

Tipranavir-ritonavir should be used in those PI-experienced patients for whom it represents the best choice of boosted PI in order to construct a maximally active antiretroviral regimen.

Let me thank you for your attention, and

turn the podium back over to Dr. Blank.

Conclusions

DR. BLANK: Thank you, Dr. Kuritzkes.

Next slide, please.

[Slide.]

We have presented to you the overview of the tipranavir development program, with the focus on the two RESIST trials.

We believe that the patient population we studied, the program that was conducted, and the trial results clearly support our request for accelerated approval for tipranavir in treatment-experienced patients.

The efficacy results clearly demonstrate greater reduction of viral load--especially, as you have heard, when tipranavir can be combined with additional active agents.

The safety data show, in general, adverse events that we have seen with other ritonavir-boosted PI regimen, with GI side effects being most frequently observed.

There are two areas where increased

adverse events were seen in the RESIST trials: LFT elevations and lipid elevations. We believe that for most patients these events can be detected by routine clinical monitoring, except for patients with chronic liver disease, where increased monitoring is needed.

Overall, we conclude that tipranavir has a favorable risk-benefit profile for PI treatment-experienced patients with drug-resistant virus. And therefore we believe that it offers a significant new treatment option for these patients.

Next slide, please.

[Slide.]

There are a number of ongoing trials which will expand our understanding on the longer term safety and efficacy of tipranavir in adults and in children.

The RESIST 1 and 2 trials are planned to continue for up to five years of follow-up. A 570 study in treatment-naive adults, and 100-patient study in children are bother fully accrued, and

data should be available early next year.

In the United States, the emergency use program remains open for adolescents between ages 13 to 18 years who need access to tipranavir. And the expanded access program remains available for treatment-experienced adults who require tipranavir to construct a viable treatment option.

BI will continue to provide tipranavir to the patients in those programs until the product is commercially available, or until it is available to world-wide or state Medicaid programs.

Next slide, please.

[Slide.]

We plan to conduct additional trials to further improve our understanding of how to administer tipranavir most effectively. This includes cohort studies in patients who are co-infected with chronic hepatitis B or C, with mild to moderate cirrhosis--including generation of more information--more data--on women.

You have heard that ritonavir-tipranavir shares chemical kinetic interactions with a number

of co-administered drugs similar to other ritonavir-PI boosted regimens. We plan a series of additional pharmacokinetic studies, including a study to understand the effect of tipranavir on individual cytochromes and p-glycoprotein in vivo; interaction studies with novel HIV drugs needed for treatment-experienced patient management; and interaction studies with commonly used medications which will become co-administered in HIV-positive patients.

Many of these studies are in the planning stage or will be initiated this year.

Next slide, please.

[Slide.]

In conclusion: we have conducted an extensive clinical trial program for tipranavir in PI-experienced, HIV-positive patients. The Phase III trials provide clear evidence of clinical benefit of tipranavir for these patients.

We believe that tipranavir meets an important clinical need, and offers hope for many patients. And therefore we propose, as an

indication that tipranavir, co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-infected patients who are protease inhibitor treatment-experienced.

This brings us to the end of our presentation, and I want to thank you for your attention.

DR. ENGLUND: Thank you very much. At this time, I'd like to schedule a coffee break.

I have a couple of short announcements here. Number one, I hope the committee here is taking notes and writing your questions down because we had a very nice and clear presentation, but we will have time for questions. I don't want you all to forget them. That's number one.

Number two: I'd like to advice the Committee to refrain from discussing this presentation and any data during the break. The weather is a good topic of conversations, may I tell you.

[Laughter.]

At this time I'd like to adjourn until

9:50. I would like to thank the company for really holding fast to the time line, and we're going to do the same for the next presentation.

Until 9:50. Thank you.

[Off the record.]

DR. ENGLUND: Back on the record.

Thank you. Thank you, everyone. Thank you very much.

We're now ready to start with the FDA presentation. And before I start, I would like to--I have been instructed to re-emphasize the blackberry point; no blackberry use inside this room, please.

We'll now start the FDA presentations. We will start with Dr. Bhore, who is getting her microphone on, and commence then, to be followed by questions from the questions. The questions that the Committee will be able to ask will be questions to both the sponsor and the FDA.

FDA Presentation

Efficacy Evaluation

DR. BHORE: Thank you, Dr. Englund. Good

morning, everyone. I'm Rafia Bhore, FDA Statistical Reviewer for the New Drug Application for tipranavir.

Today I will be presenting our evaluation of efficacy of tipranavir from the submission.

[Slide.]

Our efficacy evaluation is primary based on data from two Phase III clinical studies. First, I will discuss some details about the Phase III study, such as study design; a summary of the disposition of patients; as well as demographics and baseline characteristics of patients n the two Phase III studies.

I will also present certain aspects of the open-label study design that could impact assessment of efficacy. Then I will present the details of the evaluation of efficacy, including primary analysis; subgroup analyses for this patient population; and a head-to-head comparison of tipranavir versus other protease inhibitors, such as lopinavir, amprenavir, saquinavir and indinavir.

Finally--our summary of efficacy.

[Slide.]

The two Phase III studies of tipranavir

presented here are called "RESIST" trials, which is an acronym. Study .12 is RESIST 1, and .48 is RESIST 2.

RESIST 1 and RESIST 2 were identically designed studies with the primary difference being the geographical locations. RESIST 1 was conducted in the USA, Canada and Australia, and RESIST 2 was conducted in Europe and Latin American countries.

[Slide.]

I want to apologize for the small font on this slide in advance, but I would prefer if you focus on the main points, because this is going to be a schematic of the study designs.

Patients screened were to be three antiretroviral class and dual protease inhibitors experienced. And after screening, patients had to do genotypic resistance testing. They had to have at least primary protease resistance mutation at the protocol specified codons. If they did not,

that was a screening failure. And if they did, then they had to have less that or equal to two mutations at codons 33, 82, 84 or 90.

If they had more than two mutations, then they could enroll in the companion trial, .51, which was a slightly more advanced population. And if they satisfied these entry criteria, they could enroll in the RESIST studies.

[Slide.]

And here is the main crux of the study design. After the genotypic resistance testing was done, and based on their previous antiretroviral medication history, the investigators would pre-select the protease inhibitor for the patient. And, in addition, they would pre-select the optimized background regimen for a given patient.

After this was done, then randomization would take place. And patients would be stratified to either tipranavir or the pre-selected protease inhibitors. So, for example, if the pre-selected protease inhibitor was lopinavir, then a patient would have a 50-50 chance to get either tipranavir

or lopinavir. And the same would be true with the other protease inhibitors. And this is called "stratified randomization."

Additionally, upon FDA's recommendation, the applicant, Boehringer Ingelheim, also stratified patients based on the use of T-20. So there were two stratification factors in the study.

Once randomization was done, the study is supposed to continue through week 96. And this entire study design is open label, because of the complexity of the regimen in the control group.

An added complexity of the study design was that at Week 8, patients in the comparator group, if they had any lack of virologic response of no half-log drug, then a patient could discontinue from the comparator group and enroll in the rollover trial, .17, which would allow them to get tipranavir.

Now, this was the original schematic of the study design, which assumed that the patients in the control arm were probably getting a protease

inhibitor which, once boosted with ritonavir, would still be active and they could be treated with it. However, there was Amendment #2 to the protocol because the applicant could not enroll enough patients who were still sensitive to the protease inhibitors. And what this did is allowed the patients who had highly PI-resistant virus to be treated with boosted-PI-based regimen.

[Slide.]

Because the disposition of the patients was similar between the two RESIST studies, they're showing the disposition of patients for both studies combined, but separating by two treatment groups.

The total number of randomized and treated patients with 16 weeks of data in the tipranavir treatment group was 746, and in the comparator group was 737.

In RESIST 1, all patients would have reached 24 weeks of treatment. But in RESIST 2, not all patients would have reached 24 weeks of treatment. And therefore, our Division of

Antiviral Drug Products agreed with the applicant to accept data only on patients in RESIST 2 who would have completed 24 weeks of treatment in the RESIST 2 study. And therefore, the randomized and treated population in RESIST 1 was all of 582 patients, whereas in RESIST 2 it was a subset--I'm sorry, in the tipranavir group it was 582, and in comparator group, it was 537. But this is combined by both studies.

As you can see, there are more completers through week 24 in the tipranavir arm, which is 82 percent compared to 53 percent in the comparator arm. Or, in other words, there were more discontinuations in the comparator group than in the tipranavir group.

And the majority of these discontinuations were due to the virologic failure, or no virologic response, in the control PI s.

Among other types of discontinuation there were more discontinuations due to adverse events in the tipranavir group than in the control PI group. We will explain later that this pattern of

discontinuation due to virologic failure in the control PI arm is likely attributable to the open-label design, and due to the escape clause.

[Slide.]

The two Phase III trials were large and randomized, and we have provided you with the slides on demographics, but will not be discussing them in detail because demographics were previously described by the applicant.

[Slide.]

AS you heard previously, patients enrolling in the RESIST trials were coming in on a failing regimen. And these slides show that many patients had high viral loads, low CD4 cell count--

[Slide.]

--and had many AIDS-defining illness, and often Class C events.

More than 10 percent of the patients were also co-infected with Hepatitis B or C.

[Slide.]

At baseline, recall that genotypic resistance testing was done on patients in order to

pre-select the protease inhibitors that they would be stratified and randomized to.

In RESIST 1, genotypic testing was done based on TruGene Assay that was used to devise the categories of resistance to the protease inhibitors. And in RESIST 2, a mixture of methods was used. The European countries used Virtual Phenotype, and Latin American countries used TruGene Assay. And we think that this possibly contributed to the difference in these two subgroups: "not resistant" and "possibly resistant" between the two studies.

Also in RESIST 1, patients were more likely to receive lopinavir, while in RESIST 2, patients were likely to receive either lopinavir or amprenavir with the same probability, even though lopinavir was the preferred option for these patients.

[Slide.]

The open-label design of the RESIST 1 and 2 studies as unavoidable because of the complexity of the regimens. And we recognized that open-label

study designs can be a cause of many potential biases because of the knowledge of treatment by both the patient and the investigator.

In certain advanced patient populations, most patients on the control arm know that their virus is resistant to the control PIs and they have tipranavir as an option if they fail early.

In contrast, patients in the tipranavir arm do not have any alternatives if they fail, and this may result in different levels of compliance in the two arms.

So evaluation of efficacy therefore must account for any sources of potential open-label biases.

[Slide.]

One of the sources of bias is that although patients were randomized to receive certain treatments, the investigator or patient could change their pre-assigned study drugs that could alter the chance of success. During our review we noted that a number of patients were changing their pre-assigned regimens of enfuvirtide

or T-20.

The left side of the table shows that there were 857 patients who were not pre-assigned to take T-20. And among these patients who were not assigned to take T-20, 3 percent of the patients in the tipranavir group actually took T-20, and 1 percent in the control group took T-20.

If you look at the second type of mismatch, there were 302 patients who were assigned to take T-20, and among these, 5 percent in the tipranavir group chose not to use T-20, while in the comparator group, 16 percent chose not to use T-20.

When we compared the behavior of the patients in the comparator group in the first type of mismatch versus the second type of mismatch, we see that there is a statistically significant difference. Upon our discussion with the applicant, we found that patients who were in the comparator group did not take T-20 even when they were pre-assigned, because they wanted to take two new drugs after Week 8 through the escape clause if

their viral load did not drop.

[Slide.]

Similarly, we also saw another source of potential bias of the open-label design by noting the number of mismatches of actual versus pre-determined background regimen.

There were a total 155 combinations of pre-determined antiretroviral drugs in these trials. And the total number of actual regimens were 161. Again, the number of mismatches seen in the comparator group was slightly numerically higher in both studies.

[Slide.]

As mentioned before, there were a total of 161 combinations of antiretroviral drugs take, and the most common background combination drugs contained 3TC, ddI or tenofovir, and also abacavir and d4T with slightly less frequency.

[Slide.]

Another source of bias was the large number of protocol violations. More than half the patients in both groups had some type of protocol