DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

TOPIC:

ZIAGEN (ABACAVIR SULFATE TABLETS AND ORAL SOLUTION) FOR THE TREATMENT OF HIV INFECTION IN ADULTS AND PEDIATRIC PATIENTS 3 MONTHS OR OLDER.

GLAXO WELLCOME, INCORPORATED

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GUESTS (NONVOTING):

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C O N T E N T S

P R O C E E D I N G S

DR. MASUR [Presiding]: Good morning. I am Henry Masur. I would like to call this meeting of the Antiviral Drugs Advisory Committee meeting to order.

To begin today's hearing on Ziagen, I would like to introduce the committee. So if we could go from left to right, if each individual could introduce himself or herself and indicate his or her institutional affiliation, if any.

Jeff?

MR. BLOOM: I am Jeff Bloom. I am the AIDS patient representative.

DR. HOGAN: I am Joe Hogan. I am assistant professor in biostatistics at Brown University.

DR. WOOLSON: I am Robert Woolson. I am a professor of biostatistics at the University of Iowa College of Medicine.

DR. WONG: I am Brian Wong from Yale University.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. HAMILTON: John Hamilton, Duke University and the Durham VA Hospital.

DR. POMERANTZ: Roger Pomerantz, Thomas Jefferson University in Philadelphia.

DR. LIPSKY: Jim Lipsky, Mao Clinic, Rochester, Minnesota.

DR. El-SADR: Wafaa El-Sadr, Harlem Hospital and Columbia University.

DR. MASUR: I am Henry Masur, Critical Center, NIH.

MS. STOVER: Rhonda Stover, FDA.

DR. DIAZ: Pamela Diaz, Chicago Department of Public Health.

DR. YOGEV: Ram Yogev, Children's Memorial Hospital in Chicago and Northwestern University.

DR. GILIOTTI: Frank Giliotti, University of Rochester, Rochester, New York.

DR. ELASHOFF: Mike Elashoff, FDA.

DR. FLYER: Paul Flyer, FDA.

DR. CVETKOVICH: Therese Cvetkovich, FDA.

DR. KUKICH: Stanka Kukich, FDA.

DR. JOLSON: Heidi Jolson, director of the Division of Antiviral Products.

DR. MURPHY: Dianne Murphy, office director, Office of Drug Evaluation.

DR. MASUR: Rhonda Stover will now read the conflict of interest statements.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for conflict of interest at this meeting with the following exceptions:

In accordance with the provisions of 1896 Code 208(b), full waivers have been granted to Dr. Hamilton, Dr. Masur, and Dr. Mathews. In addition, Dr. Bertino has been granted full waiver under Section 505(n)(4) of the FD&C Act.

Further, Dr. Yogev and Dr. El-Sadr have been granted limited waivers, which permits them to participate in the committee's discussions concerning Ziagen. Dr. Yogev and Dr. El-Sadr are excluded from voting in any matters concerning Ziagen.

A copy of these waiver statements made by obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Masur is a full-time employee of the National Institutes of Health, and as a part of his federal duties, he is an investigator in the study of Ziagen as part of a salvage regimen. This is an official NIH intramural protocol. Dr. Masur is also negotiating for more studies

involving Ziagen. In the event that the discussions involve any other products or firms not already on the agenda in 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 our other participants, we ask, in the interest of fairness, that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. MASUR: Dr. Jolson will now introduce today's material.

DR. JOLSON: Good morning, and thank you, Dr. Masur, and good morning, ladies and gentlemen.

I would like to start by welcoming our returning Advisory Committee members and extend a welcome to our consultants and guests who are joining us today. I would also like to thank the sponsor, Glaxo Wellcome, for sharing the results of their studies for today's public presentation and acknowledge the children and adults who participated in the provided studies.

Since we have several new consultants and guests joining us, I thought that today's meeting might provide an appropriate opportunity to discuss two issues that are important in today's application and that are of relevance

to meetings of this Advisory Committee in general.

First, I would like to briefly summarize the process by which applications are selected for discussion at a meeting of the Antiviral Drugs Advisory Committee and, second, I would like to provide an insight into our internal review process, including how and when data are provided to the division for review.

An appreciation of both of these areas is important in understanding why we have convened this meeting and understanding the evolving nature of the abacavir database.

I would like to begin with a discussion of general criteria that the division uses in selecting applications for presentation. The Agency has no requirements to present all new drug applications at an Advisory Committee meeting and, logistically, it would be impractical and probably not productive to do so.

Therefore, the Antiviral Division carefully considers each application after its submission to determine whether discussion at an open public meeting would be beneficial.

Because these discussions occur internally, early during the review of an application our decision often leads to quite a bit of public speculation for why particular applications are brought to an Advisory Committee meeting.

Based on comments that we have received, there appear to be several misconceptions regarding how applications are selected. I would like to dispel these myths by discussing our general reasoning for determining when review of an application would benefit from public discussion. These are not hard rules, but rather represent the current thinking of the division.

No. 1, in general, drugs that are novel, such as those that are the first agents in a pharmacologic class for a given indication, will be presented at an Advisory Committee meeting. These products often represent therapeutic advances.

Two, safety. Applications that raise an important and serious safety issue are generally presented. Presentation allows the Agency to receive clinical recommendations from the committee and expedites public dissemination of important safety information.

Three, applications that raise substantive issues in the interpretation of efficacy results or that raise difficult risk-benefit questions will often be presented as a means of sharing the Agency's perspective and soliciting comments.

Four, applications that raise particularly controversial issues or that have broad public health implications would be judged to benefit from public input

and discussion and would be presented.

Five, applications where there is a fundamental and substantive disagreement between the Agency and the sponsor regarding the claim supported by data would often be presented or, at a minimum, the sponsor would be provided with this option. Unfortunately, we are rarely in this circumstance.

And, six, over-the-counter switches, which are requests to change the status of a drug from prescription to OTC status are presented in this forum. So it's reasonable to ask why we're here today and how this application fits these criteria.

Today's application is being discussed for several of the previous reasons. First, and most importantly, the application raises an important safety issue; that of hypersensitivity. Because this reaction requires prompt recognition by the provider and patient, public dissemination of this information is a priority.

Second, as will be discussed, the provided efficacy results raise several complex, analytic and risk versus benefit issues.

Third, this application features a novel aspect because it contains the first data to be reviewed by this committee on the use of a triple nucleoside analog combination regimen.

Last, although not a specific reason for presentation today, this application is also notable because it contains the first Phase III study to be conducted in a pediatric population in support of an accelerated approval for an HIV therapeutic. Promotion of pediatric drug development is a priority of the Agency. And this latter aspect of the application provides confirmation of the feasibility of conducting randomized controlled clinical trials of HIV therapeutics in pediatric age groups.

Concerns from the public are often raised that the scheduling of a meeting will delay the timely approval of a new product. I would like to provide reassurance that these meetings do not delay the approval process.

As this committee is well aware from this fall's busy schedule, meetings are scheduled with sufficient frequency, so that they may be integrated into the overall review time line for a new drug and do not delay a timely action.

My next comments are directed at the review process because our review of today's application is an example of its highly interactive nature.

One not surprising consequence of facilitating the availability of new drugs is that data submitted to FDA, in support of a new drug application, may be in various stages of completeness. From the provided background material, the

committee has been made aware that abacavir database and our understanding of the drug are an evolution.

Full study reports of results based on analyses conducted after 16 weeks of treatment in the principal abacavir studies were submitted to FDA in the original new drug application in June of this year. At the Division's request, the sponsor provided the results of these studies through 24 weeks of treatment in August. These results were requested, in part, because the Division's recent experience with other products suggest that 16 weeks may be an adequate duration of treatment with which to confidently assess an anti-retroviral treatment effect in the era of highly active anti-retroviral therapy.

In addition, the Division discussed with the sponsor several important questions that were raised during the initial review of the principal studies and inquired whether additional data from other studies were available to address these issues.

In response, the sponsor provided in October additional data based on preliminary analyses of several ongoing studies. Although we believe that this additional data is important to the committee's deliberation today, we believe that it is equally important that the early nature of its availability be well understood.

Therefore, both the sponsor and the Division will

highlight where analyses are preliminary, when available data is limited to laboratory values only, when the study remains blinded, and other instances where complete data is not yet available to the Division for review.

I would like to thank you in advance for your guidance today, and we will look forward to the committee's consideration of this application for accelerated approval.

Thank you.

DR. MASUR: The next presentation will be the sponsor presentation, which will be introduced by Dr. Smiley.

DR. SMILEY: Thank you, Drs. Masur and Jolson. On behalf of Glaxo Wellcome, we appreciate the opportunity to present data to the committee today in support of our abacavir NDAs submitted to the Agency for accelerated approval.

May I have the first slide, please?

The order of our presentations today,1 I will give an overview of the development program of abacavir, followed by Steve LaFon, who is the international project leader for abacavir, and he will present the clinical pharmacology, clinical trial results, and clinical virology data.

Following Mr. LaFon, will be Dr. Seth Hetherington, the project physician, who will review the abacavir safety profile with a particular focus on

hypersensitivity and will offer concluding comments.

Abacavir is the first new nucleoside reverse transcriptase inhibitor to be considered by the FDA since 1995. It is a carbocyclic nucleoside analog, which is activated to the triphosphate by a novel pathway. It's a potent HIV reverse transcriptase inhibitor shown in man to lead to the 1.6 to 2.1 log viral load reduction in multi-dose mono-therapy trials over 12 weeks.

Abacavir is synergistic or additive in vitro with a number of anti-retrovirals tested. Let me also add there is no bone marrow toxicity demonstrated in laboratory assays. Abacavir is orally absorbed with good CSF penetration, as shown in animal models and confirmed in man.

Abacavir is not metabolized through the cytochrome P450 pathway. Therefore, concomitant administration of drugs, such as protease inhibitors or non-nucleoside reverse transcriptase inhibitors would need no dosage adjustment.

Resistance is slow to develop in vitro and in vivo and multiple mutations are required for a six- to tenfold resistance in vitro, and this has been confirmed in vivo.

We have worked closely with the FDA over the development program of Abacavir and listed here are the key regulatory milestones. The IND was submitted in June of 1994. In January of 1997, an end-of-phase II meeting was held with the Agency, and the following month, in a closed

session of the Advisory Committee, the development strategy was reviewed and endorsed.

In March of 1997, we initiated our principal Phase III clinical studies. Let me add something that is not listed here on the slide, but it is noteworthy that in July of 19979 the committee reviewed data submitted by the surrogate marker collaborative group, which showed that suppression of HIV-RNA that is durable could correlate with clinical end points and as clinical end-point trials were becoming less feasible to conduct.

In February of 1998, we had a pre-NDA meeting with the FDA, and that month we began presubmitting our documents. In June of 1998, the full NDA was submitted, which included data from adults, as well as children, as Dr. Jolson mentioned. In October of '98, additional efficacy results of longer term data were available, including preliminary data from our equivalence study looking at an abacavir-containing regimen versus an indinavir-containing regimen, and those results will be reviewed today.

The shared understandings between Glaxo Wellcome and the FDA are listed here. As Dr. Jolson mentioned, 16-week efficacy and safety data from two adequate well-controlled trials were submitted, data from adults and children in support of our tablet and oral solution formulations. All pivotal Phase III studies were powered on

plasma HIV-RNA end points and CD4 data were monitored and collected to look for consistency with the virologic outcome.

Six-month safety summary from more than 500 patients was deemed adequate for accelerated approval, and for traditional approval, it is planned to show 48-week efficacy and safety data with efficacy focusing on durability of plasma viral load suppression and consistent CD4 responses.

This slide and the next review the scope of our development program, where we have submitted data from approximately 40 studies. The data in the NDA, which has been reviewed, includes 11 Phase I trials encompassing pharmacokinetics in adults and children, dose-ranging data, drug-drug interactions. We had seven Phase II trials. Some of these trials had as many as 100 patients going for as long as 48 weeks, and we combined abacavir with all licensed and many investigational agents, their Phase II data in adults and in children, and we focused in therapy-experienced populations, as well as therapy naive, as most of the patients are therapy-experienced right now.

Four principal Phase III trials. Data from these are included in our submission and they primarily included the investigational regimen of three nucleoside analogs; abacavir, 3TC, zidovudine.

We also have additional data from 18 either Phase II or Phase III trials, looking at other combination regimens, and these are supporting trials data in our application. In parallel, we conducted a large expanded access program targeted to children, patients with AIDS-associated dementia complex, and adults who have few therapeutic options. There are about 8,000 patients' worth of data in the submission.

It is worth taking a minute to discuss our rationale for investigating triple therapy with abacavir/3TC/zidovudine. Wherein, the potency of abacavir was demonstrated in Phase I-II trials, we elected to try it in combination with a dual nucleoside regimen of 3TC/zidovudine, just as we have done with drugs of other classes and other sponsors have done with drugs of other classes. In vitro abacavir is synergistic with zidovudine, an additive with 3TC. It does not compete with 3TC or zidovudine for activation by way of phosphorylation. Each of these three drugs terminate DNA at different sites.

There is no pharmacokinetic interaction among these three drugs, there is no overlapping toxicity. It should be a simple regimen to take, which could evolve at two pills twice a day. There are no dietary or fluid restrictions, and it is a compact regimen in hopes that it will enhance adherence and make it easier for patients.

As I mentioned before, we chose to add abacavir to a proven dual nucleoside regimen that we knew had clinical benefit. We believe the data submitted to the Agency was sufficient to support the accelerated approval of abacavir with our proposed indication statement and the label listed here.

Ziagen tablets and oral solution, in combination with other anti-retroviral agents are indicated for the treatment of HIV infection. I would like to turn it over to Mr. Steve LaFon, project leader.

MR. LaFON: Thank you, Dr. Smiley.

I would like to spend my portion of the presentation today summarizing three major programs within the abacavir development program. The first part of my presentation today will be a summary of the clinical pharmacology results that we learned in the clinical development program.

While I'll only be presenting a summary of this clinical pharmacology, Dr. Jeff Yuen, the clinical pharmacologist for the program, is with us today and, if appropriate, during the question and answer period, he can give me more clarity around any of the issues that may come up here.

The majority of my time today will be spent discussing the clinical efficacy data on abacavir. This

will primarily be data from our four Phase III clinical trials that we have conducted. And, finally, at the end of my presentation, I will be giving a short summary of the clinical virology data obtained in our clinical development program with abacavir. Again, Dr. Randall Lanier, the clinical virologist, is with us today and, if appropriate and necessary, he can go into more details of this in the question and answer period.

We conducted a very extensive clinical pharmacology program with abacavir doing studies in both adults and in children. The next two slides summarize some of the key findings from this clinical pharmacology program.

First of all, we determined that abacavir could be administered as a convenient, twice-a-day dosing regimen. We evaluated in Phase I and early Phase II trials doses of abacavir between 200 and 1,800 milligrams a day administered as either twice-a-day or three-times-a-day dosing.

Based upon the results of these trials, we determined that the optimal adult dose should be 300 milligrams administered twice a day as a 300-milligram tablet. In addition, in pediatric trials, we determined that the optimal pediatric dose should be a dose of 8 milligrams per kilogram twice a day administered as a 20-milligram-per-mL solution. We have data in clinical trials down to three months of age. We have neonate studies

ongoing at this time, no data available.

We determined in these trials that abacavir has very good absolute oral bioavailability with an oral bioavailability of 83 percent. We determined the plasma half-life of the drug was one and a half hours in clinical trials, and probably more importantly, in in vitro studies we determined that the intercellular triphosphate half-life was 3.3 hours.

In clinical pharmacology studies, we also determined that abacavir has a limited potential for drug-drug interactions. Indeed, the drug is only moderately protein bound, meaning other drugs that are highly protein bound can be safely administered with abacavir. We determined that abacavir does not have any significant P450 metabolism, meaning that it can be safely administered with other drugs that are highly metabolized by the P450 system without having to modify their dose. And, finally, we determined that abacavir really has no dietary restrictions. The drug can be administered with or without food.

Abacavir is primarily cleared from the body through metabolic processes. There are two major metabolic rounds for abacavir clearance; glucuronidation, which represents 24 to 36 percent of the administered dose and alcohol dehydrogenase, which represents up to 30 percent of the administered dose. Those two pathways together

represent approximately two-thirds of the metabolic clearance of abacavir.

In addition, there are a number of other minor metabolites, any one of which represents less than 2 percent of the administered dose. Abacavir is excreted primarily in the urine as metabolites, with 83 percent of the dose obtained in the urine. Less than 2 percent of the administered dose is excreted in the urine as intact abacavir. Indeed, another 16 percent of the dose is excreted through feces.

Finally, we learned in preclinical studies and confirmed in our clinical trials that abacavir has good CSF penetration. This data was what prompted us to conduct extensive studies in both adults and children for the activities of abacavir in patients with neurologic manifestations of HIV.

In our first multi-dose Phase 2 trial, where we administered abacavir to HIV-infected adults, treatment-naive adults, as mono-therapy initially and then in combination with zidovudine, we conducted this trial primarily to collect pharmacokinetic data and safety data, but we included into the study assessment of plasma HIV-RNA. This was our first indication that abacavir had clinical activity against HIV.

Indeed, we were pleased and surprised to find that

in all four doses administered, doses of 200 milligrams t.i.d. up to 600 milligrams t.i.d. in addition to a 300-milligram b.i.d. dose, a 1.5 to 2 log drop in plasma HIV-RNA through the first four weeks of treatment and, indeed, this response was sustained through the 12-week treatment study.

Also, we could not determine in this nonrandomized, sequentially enrolled trial, any significant difference between the four treatment groups studied. Therefore, we conducted a second Phase I dose ranging study. This trial, which is different from the first, was a randomized, blinded trial, where HIV-infected, treatment-naive adults were dosed with either 100 milligrams abacavir twice a day, 300 milligrams abacavir twice a day, or 600 milligrams twice a day.

While this study showed that the low dose, 100 milligrams b.i.d. was clearly inferior to the two higher doses, there was no difference between the 300-milligrams b.i.d. and the 600-milligrams b.i.d. with respect to median drop in plasma HIV-RNA or in respect to the proportion of patients who did not have a minimum .7 log drop in viral load by week four.

Therefore, based upon the results of these trials, we thought it appropriate to enter into Phase III development with abacavir. Today, I am going to summarize the four Phase III trials that were presented to the FDA as

part of our submission. The first three trials on this list our treatment-naive superiority trial in adults, 3003; our treatment-experienced superiority trial in children, the 3006 trial; and our study in adults with AIDS-dementia complex, 3001, were all submitted as part of our original NDA package in June of this year.

Very recently, as a matter of fact as recently as October, the preliminary results from a fourth trial that was established, we call it the treatment-naive equivalence trial, in which we compare the activity of abacavir versus indinavir in a combination treatment regimen in treatment-naive adults, this trial just recently became available in October, and we worked very closely with the FDA and with the investigators to be in a position today to present you the preliminary data from this trial.

I want to pause here just to make note of the hundreds of investigators and the literally thousands of volunteer patients who participated in these trials and in the development program of abacavir.

Three of the four trials that we'll present today have a very common treatment design. The one exception is the AIDS-dementia treatment study, which was somewhat different in design, and we'll get to that later when we describe the study.

This diagram summarizes the basic clinical design

of these Phase III trials. In the 3003, 3006, and the 3005 trial, patients were randomized into a blinded therapy, which either contained abacavir or a control arm. All studies were designed as 48-week plus trials. However, each study had built within it a 16-week planned analysis. Consistent with evolving treatment guidelines, each protocol also had built within it switch criteria, such that if patients were judged to be failing their treatment, their study treatment by either virological, immunological or clinical definitions, they were allowed to switch treatments to more appropriate and effective treatment regimens.

In addition, as Dr. Jolson had mentioned, we worked post-submission with the Agency to provide an unplanned analysis at 24 weeks for each of the studies, and we'll be presenting the results from that as well today.

Now, there is a couple of points I want to make note of that effect our adult superiority trial and the adult equivalence trial. In the adult superiority trial, we were evaluating the combination of abacavir, 3TC and zidovudine versus 3TC-zidovudine. Soon, or actually about simultaneously with the initiation of that protocol, the results of ACTG-320 became available. That trial demonstrated the clinical utility of indinavir/3TC/zidovudine.

Because of the results of that trial, we amended

Protocol 3003 to allow patients at Week 16 to switch to open-label abacavir/3TC/zidovudine. The second thing we did based upon the results of ACTG-320 was to establish a study, our equivalence trial, where we evaluated the combination of abacavir/3TC/zidovudine versus indinavir/3TC/zidovudine. As I have mentioned, we will be showing preliminary results of that trial later.

The first study I will summarize is the adult treatment-naive superiority trial. This is a randomized, double-blind trial in which 173 treatment-naive adults received either abacavir/3TC/zidovudine, or abacavir/placebo/3TC/zidovudine. All patients had to have an entry CD4 cell count of at least 100 cells per millimeter cubed. While there was no plasma HIV-RNA criteria at baseline, patients were stratified by the plasma HIV-RNA.

Both treatment groups were well-balanced at baseline with regard to median age, gender, and race. In addition, both groups, at baseline, were well matched with regard to median plasma HIV-RNA, median CD4 cell count, and disease status.

This slide summarizes the primary efficacy parameter for the study, based on an intent-to-treat analysis, where all patients were included in the analysis. The proportion of patients by treatment period, whose plasma HIV-RNA was less than 400 copies per mL, and this data

summarizes data through Week 16, the primary initial planned analysis for the study.

This analysis showed that patients randomized to abacavir, 3TC, and zidovudine had a superior response to treatment to those patients randomized at 3TC/zidovudine alone. And, indeed, at Week 16, by intent-to-treat, 75 percent of patients on the triple group, versus 35 percent of patients on the double group had plasma HIV-RNA below 400 copies per mL.

On a separate as-treated analysis, the 86 percent of patients on the triple group versus 43 percent of patients on the double group had plasma HIV-RNA less than 400 copies per mL.

This next slide summarizes the results of the Week 24 study. As we indicated earlier, this was an unplanned analysis that we worked closely with the FDA to be able to supply.

As you can see from this trial, the patients randomized originally to abacavir/3TC/zidovudine continued to maintain their viral load response out through 24 weeks of treatment. In addition, as you can see, there is an upturn in those patients originally randomized to receive 3TC and zidovudine after Week 16 of treatment. This is primarily due to the fact that most of these patients did choose to switch to open-label abacavir/3TC/zidovudine.

This slide summarizes the other efficacy parameters measured in the study. This is the median rise in baseline CD4 cell counts through 24 weeks of treatment. This analysis showed that both treatment groups have a rise in CD4 cell counts through the treatment period with no significant difference between the two treatment groups.

I want to make a special note of the Week 16 analysis. That was our planned analysis for this study. As you can see from this trial, the patients, at that time point, the patients who had received 3TC/zidovudine had a better rise in CD4 counts at that time point than did those receiving abacavir, 3TC, and zidovudine.

We have looked at this very closely, done analysis and worked with the FDA on subsequent analysis of this data. We believe this is an anomalous result, and that it is primary due to the fact that at Week 12 there is no difference in the two treatment groups and, indeed, at Week 20 and 24 there is no difference in the two treatment groups.

In addition, confirmatory to this, I will be showing you later data from the equivalence trial that shows that the CD4 response in patients receiving abacavir, 3TC, and zidovudine is essentially the same as those patients receiving indinavir, 3TC, and zidovudine.

In conclusion from this study,

abacavir/3TC/zidovudine is superior to 3TC/zidovudine in treatment-naive adults at Week 16 and 24 weeks of treatment as measured by plasma HIV-RNA.

In addition, while there is a continuous CD4 cell increase observed in both treatment groups through Week 16 and 24 weeks of treatment and there is no significant difference seen between the two treatment groups.

The next study I would like to summarize is our pediatric treatment experience superiority trial, our 3006 study. We undertook this large pediatric trial fairly early in the development of abacavir because we recognized this patient population as being one of a true, unmet medical need. Indeed, children, in general, have fewer treatment options for the treatment of HIV infection than do adults, and especially children who have already had at least some treatment for their HIV infection. Their treatment options at the time of switch are indeed extremely limited.

In general, drugs that are available for both adults and children tend to have much more of their data produced from their adult trials with usually less understanding of how to use those drugs in children than in adults.

We also felt it was very appropriate, at the time of initial submission of the NDA for a new product, that, in addition to just pharmacokinetic data being provided, that

we also have safety and efficacy data. And, indeed, this trial represents the first time that a large pediatric study was submitted as a pivotal trial to an anti-retroviral NDA for accelerated approval.

This study is an ongoing, randomized, double-blind trial in which 205 treatment-experienced children received either abacavir, 3TC, and zidovudine all in their liquid formulation form or abacavir placebo in a combination with 3TC and zidovudine. Children were stratified at baseline by age and by prior 3TC/zidovudine use. The primary end point for this study is response of HIV RNA and CD4 cell counts. However, in addition in the study, we are collecting neuropsychological end points and development milestones. While today this data is not available, it will be available at the time of the 48-week analysis.

Both treatment groups in this study were well-matched at baseline with regard to median age, gender, and race. In addition, both treatment groups were well-matched with regard to median plasma HIV-RNA, CD4 cell count, and disease status.

Some notes to take from this slide, let me point out; one, children in this trial had a fairly high plasma HIV-RNA at baseline, even though they were all on treatment at the time of starting this trial. However, we were somewhat surprised to note that a relatively high

percentage, 18 and 24 percent, actually had plasma HIV-RNA of less than 10,000 copies per mL. This is actually a very critical point because we did not anticipate this, and one of our primary analysis for the study is the percentage of patients whose viral load is less than 10,000 copies per mL. So, indeed, in this trial, 18 and 24 percent of children were already at that end point when they entered into the trial.

Our original analysis of data, we have not taken this into account, but we have done a secondary statistical analysis accounting for baseline plasma HIV-RNA. So when I discuss the results later on, I want to make sure you remember these data points.

In addition, the relatively high CD4 cell count in this study, when you compare this to an adult trial, should not be misleading, in that children tend to have higher CD4s than adults. And, indeed, approximately a quarter of the patients in the trial entered this trial with a CDC classification considered severely symptomatic. And, indeed, more than half the patients in each treatment group had received greater than two years of prior anti-retroviral therapy.

This slide summarizes the primary efficacy parameters in the trial. The proportion of patients whose viral load dropped less than 10,000 copies per mL and less

than 400 copies per mL through 24 weeks of treatment. In both analyses, the patients who received abacavir/3TC/zidovudine had a superior response to the patients who had received 3TC and zidovudine alone.

I want to make particular focus on this time point for just a minute because I mentioned earlier the primary efficacy analysis of the proportion of patients less than 10,000 copies per mL, at this time point, without adjusting for baseline viral load, had a P value of .054. So marginally statistically significant. However, when baseline plasma HIV-RNA was accounted for in the statistical analysis, the P value adjusted for that variable was .006.

I should make a note at this time, patients were prestratified by age, and there is no substantial difference between the children who were less than 30 months of age and those who were greater than 30 months of age.

This slide summarizes the CD4 cell response in the two treatment groups. The patients who received abacavir, zidovudine, and 3TC had a superior CD4 cell count rise over 24 weeks of treatment compared to those children who received 3TC and zidovudine alone.

I will note that we have also done this analysis using CD4 percent, which is a more typical analysis pediatricians are used to, and we saw similar results with a better response in the triple group than in the double

group.

So, in conclusion from this study, abacavir, 3TC, and zidovudine is superior to 3TC/zidovudine in heavily pretreated children through 16 to 24 weeks of treatment, as measured by plasma HIV-RNA. In addition, the CD4 cell increase was superior in the abacavir, 3TC, zidovudine arm, and that was actually remarkable considering there was no difference in the adult trial that I previously described.

However, we did learn from this trial that the response, at least the response in plasma HIV-RNA to abacavir, 3TC, and zidovudine may be diminished in heavily pretreated children when compared to treatment-naive adults. I will add that we have done a pilot study in heavily pretreated adults. We saw very similar results to this trial, and our conclusion from that is the activity of abacavir in children and in adults is very similar.

We briefly want to now explain, summarize the trial we did in adults with AIDS dementia complex. I had mentioned earlier we undertook this trial because of the early preclinical data and clinical data showing that abacavir did penetrate into the Central Nervous System very well.

The design of this trial, this was a randomized, double-blind study of patients with mild to moderate AIDS dementia complex. 99 adults were randomized to either

receive abacavir at a dose of 600 milligrams b.i.d., twice the dose that we are using in our other adult studies. We actually chose this dose to maximize the penetration into the CNS.

Again, the patients are randomized to either abacavir, in addition to their stable background therapy, abacavir placebo. The primary end point in this study, different from our other trials, was changes in neuropsychological performance measured as NPZ scores at 12 weeks of treatment. After 12 weeks of treatment, all patients were offered open-labeled abacavir.

The results of this trial, surprisingly, both treatment groups, the group that received abacavir and the group that received abacavir placebo had a positive response on neuropscyh nucleoside scores at Week 12 of treatment. However, there was no significant difference in the two treatment groups. Based upon the results of this trial, we have not submitted to the FDA for an indication specifically for the treatment of AIDS dementia complex.

I will, as I have mentioned earlier, we are conducting similar studies in the pediatric trial. Those results will be available at Week 48 of treatment and, hopefully, will give us more information about the use of this drug in patients with neurological manifestations of HIV.

Finally, as I mentioned earlier, we now are in a position today to present preliminary results from our study, our adult treatment-naive equivalence trial, our 3005 trial. I have mentioned earlier that this is an ongoing study, and we have worked closely with both the Agency and with the investigators to be able to present this today. This is an ongoing, randomized, double-blind trial. 562 treatment-naive adults were randomized to either receive abacavir, 3TC and zidovudine or indinavir, administered at 800 milligrams every eight hours, and 3TC and zidovudine.

I want to mention this is actually a very large study. The size of the study is larger than all three of the other trials we have just presented combined.

I also want to, at this time, acknowledge Merck, who provided both the indinavir and the indinavir placebo for this trial.

I should mention all patients received matched placebo for abacavir and indinavir, meaning the abacavir patients also received indinavir placebo and the indinavir patients received abacavir placebo.

Also, patients had to adhere to the indinavir diet restrictions and the fluid requirements required for the administration of that product.

In addition, the plasma HIV-RNA at entry was required to be at least 10,000 copies per mL and CD4 cell

counts were supposed to be at least 100 cells per cubic millimeter.

The primary analysis for this trial is actually to demonstrate equivalence between the two treatment arms at Week 48 of treatment. However, we did have a planned 16-week analysis, which we are presenting today. Indeed, we are going to be, in order to maintain the integrity of this blinded trial, we are actually presenting this data today as Treatment A or Treatment B. We will not be unblinding the treatments in the presentation today.

This study today will present preliminary analysis of select efficacy data as of October of this month. At the time of this analysis, 95 percent of the patients, randomized to the trial, had received 16 weeks of treatment and 85 percent of the patients had received 24 weeks of treatment.

Both the randomization was equal or fairly equal between the two treatment groups. Treatment A enrolled 280 patients, Treatment B, 282 patients. By Week 16 of treatment and by Week 24 of treatment, there was a similar proportion of patients discontinuing therapy prematurely and, indeed, the primary reason for discontinuation was adverse events, and there was a very similar number of patients discontinuing, by Week 24, due to adverse events in the two treatment groups.

Both treatment groups were well-matched at baseline by median age, by gender, and by race. In addition, both treatment groups were well-matched at baseline by plasma HIV-RNA, by median CD4 cell count, and by disease status.

Just to contrast this study with our 3003 trial, the trial I presented earlier, these patients, in general, had slightly higher plasma HIV-RNA at baseline, the 3003 median baseline, plasma HIV-RNA was approximately 4.5 logs and, indeed, had lower CD4 cell counts at baseline, and the 3003 results median CD4 cell count were approximately 450.

This slide summarizes the preliminary results from this trial through 24 weeks of treatment. This is an intent-to-treat analysis of the proportion of patients whose plasma HIV-RNA is less than 400 copies per mL by each time point through 24 weeks.

As you can see from the graph, after a slight divergence in the early parts of the treatment, both treatment groups had the, essentially, identical proportion of patients, less than 400 copies per mL, through 24 weeks of treatment. By intent-to-treat analysis at Week 24, 60 percent of patients in each treatment group had plasma HIV-RNA less than 400 copies per mL.

The on-treatment analysis at 24 weeks of treatment, both treatment groups had 85 percent of patients

below 400 copies per mL.

This slide summarizes the median CD4 cell count response in the two treatment groups, again, through 24 weeks of treatment. As you can see, both treatment groups had a very rapid rise in CD4 cell counts initially in treatment, but then a continued and more gradual rise in CD4 cell counts after 24 weeks of treatment. There is no difference in the two treatment groups with regard to CD4 cell count response. And, indeed, by Week 24 of treatment, both groups, essentially, had about a 100-cell rise in CD4 cell counts.

In summary from this trial, from the preliminary findings from this trial, abacavir/3TC/zidovudine and indinavir/3TC/zidovudine demonstrate an equivalent virological response and equivalent CD4 increases through 24 weeks of treatment. The study also showed similar rates of discontinuation observed in both treatment groups through 24 weeks of treatment, including discontinuations due to adverse events, which were similar in both treatment groups.

And, finally, as I have mentioned earlier, this study remains blinded, and ongoing, and it will continue until the last patient randomized reaches at least 48 weeks of treatment.

Now I didn't have time to present the results of other studies today. I just wanted to make note of the fact

that we are conducting and have conducted a number of other trials using abacavir in various different combinations and in different patient populations in treatment-naive adults, and treatment-experienced patients, and in combination with protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Most of these studies, but not all of these studies, most of these studies have been submitted, at least preliminary results of these studies, have been submitted to the Agency, and several of them, indeed, are summarized in your briefing document that you have today.

I want to make note of a couple of studies. Just to point out, the 2004 study was a trial of abacavir in combination with all of the marketed protease inhibitors and, indeed, one protease inhibitor in late-phase development imprimavir [ph.] in treatment-naive adults. This trial, which we now actually have data through 48 weeks of treatment, shows that abacavir can be safely administered with other protease inhibitors and, indeed, the virological response of abacavir plus protease inhibitors was very good and sustained throughout the treatment period.

Another study to make note of is a study combining the tree most recently developed new drugs; abacavir, which we are discussing today, imprimavir, which is in late-phase development and, indeed, an NDA was recently submitted to

the Agency, and efavirenz, the non-nucleoside reverse transcriptase inhibitor, which was recently approved.

This study combined these three drugs for treatment of treatment-experienced adults and, indeed, these were patients who had failed multiple therapies with all patients having experience with both nucleoside reverse-transcriptase inhibitors and protease inhibitors, and half of the patients actually previously treated with non-nucleoside reverse transcriptase inhibitors. And this study did show that these drugs could be administered together, and at least in some patients within the population did get a very good viral load response.

In addition, there are three trials that are rollover trials from the original ACTG-320 study, where we evaluate abacavir in combination with efavirenz and indinavir and patients who were originally on 3TC and zidovudine in that trial. We also evaluated abacavir as an intensification strategy in patients whose viral load is less than 500 copies per mL, while on 3TC, zidovudine, and indinavir and, finally, a trial looking at patients who had been originally on 3TC, zidovudine, and indinavir, but, indeed, were judged to be failing that treatment regimen, where adefovir, efavirenz, nelfinavir, and abacavir or two new nucleosides have been evaluated.

So, in conclusion, from our efficacy studies,

anti-retroviral activity of abacavir has been demonstrated in both adults and pediatric populations. The anti-retroviral benefit of abacavir has been demonstrated in treatment-naive and treatment-experienced patients. Note the results from the equivalence trials suggest that the abacavir activity in naive patients is, indeed, remarkable and at least preliminary results looks like it is similar in activity to indinavir in that population.

We have demonstrated in a number of treatment-experienced studies that the anti-retroviral effect of abacavir may be attenuated in some treatment-experienced patients. This is not unusual, in that other nucleoside reverse transcriptase inhibitors have less of an effect in patients who have already been previously treated with a class of drugs.

And, finally, abacavir, in combination with other anti-retroviral agents, is a highly effective treatment for HIV infection.

Briefly, my next two slides will summarize the clinical virology program that we undertook for this drug. Before going into the clinic, we actually conducted extensive in vitro studies to both define the resistance and the cross-resistance profile of abacavir. We took learnings from these trials to take into our clinical efficacy studies, in which we conducted significant clinical virology

substudies as part of all of our Phase 2 and our Phase 3 clinical trials. In these substudies, we determined viral genotype and phenotype sensitivity at baseline and on treatment, as appropriate, and at least a subset of patients in all of the Phase 2 and 3 trials, and in some cases, in all of the patients in these trials.

We also attempted to make correlates between the viral genotype and phenotype at baseline with the HIV RNA response. While this work is continuing ongoing, the data is preliminary, Glaxo Wellcome is committed to continue to do this work to confirm the preliminary data and to examine the effect of abacavir treatment and subsequent therapies.

This next slide actually summarizes some of the key findings from our clinical virology program. We learned in preclinical studies that the RT mutations are selected for abacavir on exposure to abacavir in vitro. These are specifically mutations at sites 65, 74, 115, and 184. And, indeed, in clinical studies of patients exposed to abacavir, we have seen clinical isolates with at least one of the--we have seen all of these point mutations observed in clinical isolates, with the most frequently observed being the 184 mutation and the 74 mutation.

Notably, there have been no new RT mutations observed in patients treated with abacavir beyond the four we saw in preclinical development.

We also learned in clinical virology studies that no single baseline RT mutation predicts a lack of response to abacavir. And, indeed, this is especially true of the 184 mutation, which we have extensively studied.

Finally, we have also learned that multiple baseline RT mutations can be associated with diminished response to abacavir. While we continue this work, and we're actually collaborating with a number of investigators and a number of other companies, the clinical utility of resistance testing to predict response to abacavir requires further evaluation.

I would next like to turn the microphone over to Dr. Seth Hetherington, who will come up and give an overview of the safety profile of abacavir.

DR. HETHERINGTON: Thank you for the opportunity to describe the safety profile of abacavir. This talk will take three parts.

First, I am going to discuss the safety data from the controlled clinical trials of the efficacy data that you have just seen.

Next, I am going to discuss, briefly, the expanded access program. Remember, that this is still ongoing. The data is not monitored, and it has not been quality assured.

And, finally, I am going to review in detail the hypersensitivity reaction that some patients experience with

abacavir, and I will cover both recognition and management.

Now, the Phase 2 and Phase 3 studies, as submitted in the NDA, include information on 723 patients. This does not include the data from the 3005 study, since this data, again, is still preliminary, but I will restrict my comments to the Phase 3 trials that you have just heard about.

Among those 723 patients, 578 have experienced treatment with abacavir for at least 24 weeks and another 144 patients of these have been treated for a minimum of 48 weeks.

First, let's look at the column "Clinical Adverse Events" that occurred in the treatment-naive trial 3003, among adults.

What I show here are the results from patients in the abacavir arm and in the control arm, and I list the most common adverse events here. The first thing you will notice is that the most common adverse events are primarily related to the gastrointestinal tract. This includes nausea, nausea and vomiting, and diarrhea. You will also notice that events of all grades, grades 1 through 4, as determined by the ACTG clinical toxicity tables, occur with similar frequencies between both the abacavir and the control arms. None of these numbers are statistically significant.

You will also notice that patients do experience or report some constitutional symptoms, primarily malaise,

and fatigue and headache. Again, the numbers are similar and not statistically significantly different between the abacavir and the control arms.

Finally, I would like to point out that among the severe events; that is, those grade 3 and 4, there is absolutely no difference in the incidence between the two treatment arms. These are very infrequent and rarely are they treatment limiting.

Let's compare that to the pediatric trial 3006. Overall, the pattern is extremely similar to what you have just seen. Again, I show you the abacavir arm and the control arm. Gastrointestinal symptoms, primarily nausea, and vomiting, and diarrhea, are very frequent among participants, but that includes events of all grades. There is a statistically significant difference in nausea and vomiting, as reported by those patients receiving abacavir and those receiving the control arm. What you will also see is that the severe events, again, are very infrequent and are not often treatment-limiting between the two arms.

The other common events that you see in the pediatric trial are related to upper-respiratory tract infections, such as earn, nose, and throat infections, cough, and fever. These are of similar frequency across both arms, with the exception of cough. We don't have an explanation for this, but overall we feel that these events

are primarily related to the common illnesses of childhood and not drug related.

Now, the 3001 trial allows us the opportunity to look at the adverse event profile of abacavir at a higher dose. Remember, this is 600 milligrams b.i.d. in contrast to 300 milligrams b.i.d. in the 3003 adult-naive treatment trial.

Again, you see the same kinds of adverse events listed, primarily of the gastrointestinal tract, with nausea, diarrhea being predominant. You also see constitutional symptoms, such as malaise, and fatigue, and headache. The incidence of these events across the arms is similar, with an at least numerical greater frequency of nausea in the abacavir compared to the background treatment group.

This trial also had a reported neuropathy in equal amounts between both treatment arms. This is probably related to the background treatment. And this trial, unlike the others, these patients, a large proportion of them, were receiving protease inhibitors or other medications known to cause neuropathy.

You will also notice that the severe events of grade 3 and 4 are similar across both arms and relatively infrequent.

I would now like to turn to the treatment-

emergent, grade 3 and 4 laboratory abnormalities, as demonstrated in the adult treatment trial 3003. We have these broken down by organ systems.

You will notice that, overall, there is no difference between the two groups for any of these events, with the exception of CPK, and I will get to that in a minute. But, primarily, there is no evidence of bone marrow suppression, as demonstrated by the frequencies of anemia and neutropenia for both treatment arms. There is no evidence for hepatic toxicity. As you will notice, the elevations in ALT, ASD, and alkaline phosphatase are similar across both treatment arms. There is no evidence of pancreatitis being significantly different between the two treatment arms, and there is no evidence of renal compromise in either treatment group.

You do see elevated CPK as the most common laboratory abnormality noted for both treatment arms. This is most likely related to exercise. Very rarely, if ever, was CPK the reason for discontinuing therapy. In fact, these elevations of CPK were almost always asymptomatic.

Let's compare that now to the treatment-emergent grade 3/4 laboratory abnormalities seen among children treated with abacavir. Again, I have this broken down into the same organ systems. You will see that there is no difference in the frequencies of anemia and neutropenia,

both of which were very infrequent for both the abacavir and the control arms. There is also no evidence for abnormalities among the hepatic or pancreatic system being different between both treatment groups. And, finally, hyperbilirubinemia exhibited only in two patients in the abacavir arm and one in zidovudine/3TC arm. So, in general, you see the same kind of pattern that we observed for adults.

Again, the 3001 trial allows us to look at the frequency of laboratory abnormalities among patients receiving twice the dose of that received in the adult trial 3003. There are 49 patients in the abacavir arm and 50 in the background arm. And, again, you will see for evidence of bone marrow suppression, really, no difference between the two treatment groups, no difference in elevation of liver function tests across the groups, no difference in elevations of CPK or amylase. Again, you do see elevation of triviscerides [ph.]. We believe that this is related to the background therapy, since the incidence is identical in both the abacavir and in the placebo-receiving arm.

Let me briefly go over the expanded access program and orient you a little bit. We initiated the open-label expanded access program in two stages; in response to requests for access to abacavir by patients who had fewer or no options, we started the open-label program in July of

1997. At that time, we had safety data on only approximately 200 patients.

Once more data was available, we did open up the expanded-access program in March of this year, and what you will notice is that there are very different requirements for both groups. The open-label program was far more restricted. It had HIV RNA and CD4 criteria. It was restricted to certain geographical sites, and it also had an enrollment of about 2,000 patients over that time.

By contrast, the expanded access program, which opened up in March, had a far more open-entry criteria. It was left to the patient and physician to decide if abacavir was required for subsequent regimen. There were no virologic or immunologic entry criteria. As of July 14th of this year, we have enrolled 6,922 subjects--that number is now in excess of 11,000 today--and it did include patients who had rolled over from the open-label program.

Let's look only at the open-label program, since this data was collected in a far more far-reaching manner than the expanded access program. Again, we had just over 2,000 patients enrolled. Of those patients, we have follow-up data available on 1,677 patients at the time that we submitted our new drug application. 376 of those patients have permanently discontinued. The most common reason was an adverse event, and then there are a scattering of reasons

that you see below.

Among these patients, the most common adverse events occurring among the 1,677 patients are listed here. Again, you see the same kind of pattern that you saw in our Phase 3 control trials; that is, gastrointestinal symptoms are the most frequently reported, along with some constitutional symptoms, such as malaise, and fatigue and, in this case, fever and chills.

You will note the incidence of rashes appears at 15 percent. These patients were receiving broad categories of therapies, multiple drugs, including non-nucleoside reverse transcriptase inhibitors in approximately 40 percent of the cases. This incidence, by the way, is identical to the placebo arm in one of the early zidovudine control trials. So we do not believe that that 15 percent is particularly unusual.

Let me turn, briefly, to give you a summary of the mortality that has occurred in not only the clinical studies, but in the expanded access patients. That total patient population is 8,000 as of July 1998. I have divided this slide into several sections. First of all, the randomized phase, as applicable to Phase 2 and 3 trials, and then the open-label phase for those same trials. The expanded access trial is listed only as an open-label trial, obviously. And I have included other trials, such as ACTG-

368, and the pediatric and AIDS dementia expanded access programs, which were far smaller than the major expanded access program.

What you will see is that, during the randomized phase for all of our Phase 2 and 3 studies, there were an equal number of deaths that occurred in the abacavir and in the control arms. I want to point that one patient in the 3005 trial did die of an abacavir-related hypersensitivity reaction upon rechallenge of the drug, and I will give you more details on that in a little bit.

In the open-label phase, we did see six deaths in the advanced disease patient populations included in the AIDS dementia trial 3001. The vast majority of deaths, however, that have occurred among all of our studies, among these 8,000 patients, is 133 in the expanded access program. The vast majority of these are due to either disease progression or complications of HIV disease.

Now, we are all aware that the FDA has raised questions about seven additional patients in here, as to whether not these are related to abacavir hypersensitivity. I have reviewed these clinical cases. I have spoken to many of the physicians during the time that these cases have appeared. We have not had the opportunity to discuss these cases with the FDA, but I will say that on careful review, these cases do not hold together as episodes of

hypersensitivity reactions. I am ready to present these cases and discuss them if the committee so desires.

The key point I want to make, and I will in a minute, about abacavir hypersensitivity is that it has a broad definition that allows for evolution of this clinical description as our experience grows. The interpretation of these or other cases may change as that experience grows. But the key point, again, is that we will continue to work with the FDA and physicians to continue to collect data on abacavir hypersensitivity and to analyze these cases to enhance the ability of physicians to recognize and manage these cases.

Let me just back up a minute and summarize the safety before I do get into a detailed discussion of abacavir hypersensitivity. First of all, as you have seen, the most common adverse experiences seen with abacavir therapy are nausea, and malaise and fatigue. And, in fact, on analysis of pooling the Phase 3 data, these are the only adverse events among the common ones listed that turn out to have a statistical significance risk factor for abacavir.

Most of these events are mild to moderate, and they are transient. They are rarely treatment limiting. It's very important to note that the safety profile of abacavir is similar in adults and in children. And, finally, there is no evidence in our Phase 2 or 3 trials for

hematologic, pancreatic, hepatic or renal laboratory abnormalities associated with abacavir therapy.

Let's turn now to the clinical description of abacavir hypersensitivity. This is, in general, can be described as a multi-organ reaction that usually occurs within the first six weeks of therapy. It occurred in 17 of the 723 subjects exposed to abacavir in the Phase 2 and 3 trials for an incidence of 2.3 percent. In the expanded access program among 6,922 patients as of the July 20th safety update, we have approximately 3 percent incidence.

Now, the presentation of abacavir hypersensitivity is varied, but the most common clinical presentation are the four symptoms of fever, rash, malaise and fatigue, and nausea, with or without vomiting.

I use two case definitions in review of abacavir hypersensitivity. The first one is the definitive case. This presents as an initial multi-system constellation of symptoms that occurs on rechallenge of the drug. And this we have approximately 30 cases that I am going to review for you today.

In addition, there are those probable cases. These are 69 cases in which the symptoms were consistent with a syndrome as demonstrated by the definitive cases, but in which no rechallenge was done.

So what are the symptoms and signs of abacavir

hypersensitivity? They are shown for you here for both the definitive cases and the probable cases in decreasing order of frequency. Fever is the most common symptom that is reported by patients in the vast majority of patients. It generally begins low grade, but can build with continued dosing over several days. Rash may follow the development of fever or may occur concurrently. This rash tends to be macular papillar, it can be urticarial, but it's generally mild, and it's rarely the reason that patients come to the attention of their physician.

Constitutional symptoms are very common. And patients, it's very helpful to note, will give a history of increase in severity of malaise and fatigue over the course of several days, sometimes coincident with the administration of abacavir.

Gastrointestinal symptoms, such as nausea and vomiting, sometimes diarrhea, and sometimes abdominal pain are also common when this syndrome presents.

Mouth and throat symptoms primarily consist of mouth ulcers, which is not unusual in the clinical presentation of a hypersensitivity reaction. Respiratory symptoms tend to be vague. Patients usually, if they report any such symptoms, record them as a general feeling of shortness of breath, sometimes pressure in the chest. But bronchospasm is distinctly unusual or even absent.

Musculoskeletal complaints consist primarily of arthralgias and myalgias. And, finally, it's important to note that about 7 percent of patients, both in the probable and the definitive cases, have presented with hypotension at the time of initial presentation.

Let's look at the time to onset of abacavir hypersensitivity because this is very useful. Again, I am showing you the definite cases. We have times recorded for 27 of those, and among the probable cases, 67 have the time of onset noted.

All of the definitive cases occurred within the first five to six weeks of therapy. Similarly, you see the vast majority of probable cases occurring in that time frame. The median time to onset for all of these cases is 11 days.

Among the probable cases, there are a few that occur after six weeks, and these are scattered over time. These may represent true cases of hypersensitivity, they could be reactions to other medications, or they could be inoccurrent illnesses.

The laboratory abnormalities that occur with abacavir hypersensitivity are nonspecific and not diagnostic, but they are important to be aware of.

First of all, these are recorded only if laboratory studies are obtained at the time of the acute or

rechallenge with abacavir, and that is not always done. So these are probably well underreported.

Elevation of liver enzymes can occur typical with hypersensitivity reactions to other drugs. This is an anicteric hepatitis type of picture with mild to moderate elevation of liver function tests.

Lymphopenia is very common, at least when the CBC has been obtained. It's most likely a redistribution effect because once you stop the drug and recheck the white blood cell count and differential a week later, these numbers are back to baseline. Elevations of CPK have been recorded less frequently, but they might be very pronounced in those patients who report myalgias.

Thrombocytopenia has been mild in a few patients. This is not clinically significant. I have never seen a reported number go below 50,000 per millimeter cubed.

It's important to remember that all of these laboratory abnormalities will resolve within days of discontinuing abacavir.

Let me point out some clinical aspects of hypersensitivity to abacavir that might be helpful. I have already mentioned that continued dosing in the face of an abacavir hypersensitivity reaction will result in a worsening of symptoms, and the vast majority of cases have presented with really several days of ongoing symptoms. If

you can get the patient to tell you what the timing is of these occurrences with their dosing, it might be very helpful.

Secondly, stopping abacavir leads to a very rapid resolution in the hypersensitivity symptoms, and this is quite remarkable how much improved these patients are within 24 to 48 hours. Restarting abacavir after stopping for a hypersensitivity reaction may lead to more severe and potentially life-threatening events, including death, associated with a recurrence of a hypersensitivity reaction.

I do want you to recognize that the abacavir hypersensitivity has been well characterized through the data I have just presented, and it's really diagnosable through the tools that are available to all clinicians; that is, a good history and physical and, finally, it is manageable simply by stopping the abacavir.

Let me make some observations on the management of abacavir hypersensitivity that might be useful. First of all, patients and physicians should be familiar with the signs and symptoms of abacavir hypersensitivity before embarking on a treatment regimen that includes abacavir. Consider the diagnosis of hypersensitivity when patients present with fever, plus evidence of organ system involvement or evidence of two or more organ system abnormalities.

The diagnosis is based on the clinical presentation. A single organ system involvement, particularly rash, you can advise to continue the abacavir with careful follow-up as long as the patient is aware of what other symptoms to look for and contacts the physician and stops the abacavir once other symptoms present. This is particularly useful for those patients that are receiving abacavir plus a non-nucleoside reverse transcriptase inhibitor. We've used this strategy in the open label and expanded access programs with exceedingly good results.

Cardinal rule, when the differentiation from inoccurrent illness or other drug reaction is not possible, stop the abacavir, and that's a rule that we've emphasized again and again in all of our treatment trials and the expanded access program.

Risk factors for the development of abacavir hypersensitivity are not known. It has occurred at all doses with all regimens tested. The frequency and clinical presentation are identical between adults and children. It occurs with all combinations of anti-retroviral agents. We do not see an increase in abacavir hypersensitivity when it's been combined with non-nucleoside reverse transcriptase inhibitors or any particular combination. Similarly, we do not see an impact of abacavir on the frequency of rash with other anti-retroviral agents.

The range of incidence across all of our protocols is anywhere from zero to 5 percent. Obviously, that is statistical variation. I think the correct number is that abacavir hypersensitivity will occur in approximately 3 percent of patients that initiate therapy with abacavir.

Let me now summarize the safety conclusions about abacavir. First, the most common adverse experiences are mild to moderate, they are transient in nature, and they are rarely treatment limiting. Adverse events common to other nucleoside reverse transcript inhibitors, such as pancreatitis, neuropathy, anemia, or neutropenia, are not seen with abacavir. And, finally, abacavir hypersensitivity is the most significant adverse event leading to discontinuation with an incidence of approximate 3 percent.

I would now like to close the Glaxo Wellcome presentation on abacavir with a few concluding remarks.

First of all, we have ongoing studies for the traditional approval of abacavir. This is based on 48-week data, which will demonstrate durable surrogate marker responses. Those trials that we have in this category include the adult treatment-naive equivalence trial, 3005; the pediatric treatment experience trial, 3006; and, finally, the adult treatment naive trial, 3003.

Our data has shown that abacavir has potent intrinsic anti-retroviral activity. It can be provided in a

convenient b.i.d. dosing. Its metabolism shows that it has limited potential for drug-drug interactions, although those studies looking at various combinations are in progress.

There are no dietary restrictions for the use of abacavir, and it's been shown in preliminary data from the 3005 trial suggests that the triple nucleoside reverse transcriptase inhibitor combination strategy may be reasonable for some patients.

We do have evidence that abacavir is active in therapy-experienced patients. As with other nucleosides or any anti-retroviral therapy, patients with prior therapy with drugs of the same class may have an attenuated response. It is, however, well-tolerated in combination with other anti-retrovirals, and it is a good candidate as part of a multi-drug combination regimen.

Finally, the data we have provided to the FDA that are summarized today demonstrate that the risk-benefit analysis is clearly in favor of the approval of abacavir therapy for the treatment of HIV 1 infection.

Thank you very much. That ends our presentation.

DR. MASUR: At this point, let's see what questions the committee members have. Maybe we'll start from right to left. Frank, do you have issues you want to bring up?

DR. GIGLIOTTI: No.

DR. MASUR: Nothing. Ron?

DR. YOGEV: I was intrigued by the CSF penetration, supposedly 30 to 40 percent, and in what I got it is supposedly only from three patients; am I correct on that?

MR. LaFON: No. We've conducted, actually, early on in our adult trial with just a small number of patients, but then we conducted more rigorous CSF penetration study as one of our Phase 1 trials, and I am going to have to have a reminder of how many patients were involved in the--

DR. YUEN: There were three.

MR. LaFON: Okay. You are correct. It's only three. It was an 18-patient study, but it was a voluntary CSF collection.

DR. YOGEV: When you mention 30 percent are you talking area of the curve or are you talking about peak level in the blood versus peak level in the CSF?

DR. YUEN: The study we are talking about is our mass balance study, and what we did was take serial CSF levels and plasma levels simultaneously out to six hours. Based on those levels and the area under the curve for both CSF and plasma, we calculated the penetration. We also have additional data from single time points in our dementia trial, and we are analyzing those data now.

DR. MASUR: For the sake of the record, could you

identify yourself.

DR. YUEN: This is Dr. Yuen from Glaxo Wellcome, the clinical pharmacologist.

DR. YOGEV: Another question. There was a study in the ACTG-330 I think that was prematurely struck. Are there any data available on that?

MR. LaFON: That was a pharmacokinetic trial, a multi-dose pharmacokinetic trial, the first multi-dose trial we conducted in children, and there was data submitted to the Agency on that, both pharmacokinetic safety and preliminary efficacy viral load response. Yes, there is data. The bottom-line results from that is we demonstrated the pharmacokinetics of the study that was from that trial and other single-dose trials that an 8 milligram per kilogram b.i.d. dose would be appropriate.

That study, from an efficacy perspective, did not show an activity of abacavir in that population. However, that was a population that received fairly long-term prior therapy with nucleosides. I don't remember the median duration, but it was three to five years treatment with prior nucleosides prior to coming into the study.

DR. YOGEV: And the last question is: I understand in pediatric 50 percent about were more than two years on AZT and 3TC, and I just wonder did you do any subanalysis of those who got less than several months

because otherwise I think we are comparing mono-therapy.

MR. LaFON: There were more than two years of prior treatment with anti-retroviral therapy, not necessarily 3TC and, actually, we did look--actually, more than 80 percent of the patients had received 3TC, and I think more than 50 percent had received--I am sorry, had received zidovudine and more than 50 percent had received 3TC.

The study was designed with a prestratification based upon prior 3TC/zidovudine use and the last six months were not. And the results of that show that the patients who had not received 3TC/zidovudine in the last six months responded much better to abacavir/3TC/zidovudine than those patients who had received 3TC/zidovudine in the last six months.

DR. YOGEV: And when you compare those patients to the triple nucleoside therapy, those who responded better, was there still the difference or not?

MR. LaFON: The difference between the triple therapy and the double therapy was not apparent in the patients who had received prior 3TC/zidovudine in the last six months.

DR. MASUR: Pam?

DR. DIAZ: I have several questions actually regarding the hypersensitivity reactions as probably other

members do. We can either go into those now or--

In particular I was interested in just a little bit more information about patients with hypersensitivity reactions and especially those patients who died.

Things, information regarding which trials, in particular, they span over, their age ranges, the pediatric patients versus the adult patients, and especially information regarding more experienced patients. There seem to be a higher percentage of those patients with rash and if that contributed in those more therapy-experienced patients to a higher incidence of hypersensitivity.

And how far these patients go before they are able to go with therapy before our decision is made because many of the symptoms such as nausea, vomiting, fever, et cetera, as you pointed out, are symptoms that are commonly found with inter-occurring infections with other therapy. And in particular, in terms of the deaths, did the deaths occur in the face of having stopped the abacavir or did the deaths occur in patients who are continued on therapy unrecognized as a hypersensitivity reaction?

DR. MASUR: Yes. This also might be a good opportunity, since you offered to provide more data on the possible or probable deaths, to give us a little more data on those patients, if you will?

DR. HEATHERINGTON: Okay. I am happy to do that.

There are a number of questions that you raised in there and I seriously doubt I am going to remember all of them. So, you're going to have to back me up a little bit if I don't catch them all.

But let me get some of the easier questions out of the way first, and then we can go through some of the cases.

First of all, you asked about the ages of presentation. The frequency is similar in adults and children. In fact, it's just about dead on. It's about 2 or 3 percent in both age groups.

You asked about patients who are more advanced versus those who are less advanced and we don't have any evidence on reviewing protocol by protocol that the frequency differs with the stage of disease.

In fact, it's interesting in our inter-age dimension trial, which was in the phase three trials, represents the most advanced diseased patients. There was only one among the 49 patients in the abacavir arm that had a hypersensitivity reaction.

So, I don't think that we have any clues from either the age or demographics of the patients or the stage of disease which indicates a likelihood of reaction.

You did make a statement that it seemed to be more frequent in the advanced disease patients and I don't think that is correct. I think in our analysis it looks like it's

pretty much the same. Maybe I misunderstood you.

DR. DIAZ: Just rash.

DR. HEATHERINGTON: Actually we did not look at the frequency of rash as part of the constellation of symptoms by disease state. We did not do that. What you might be referring to is the fact that in the expanded access program 15 percent of patients report rash at some time, but if you look at the times of onset those are usually isolated events and far out beyond the six weeks of therapy. Actually we did look at that earlier and it's pretty easy to tell the difference.

I tried to stress all along that rash is not the determining characteristic of this reaction. As you can imagine early on in our understanding of this, it seemed to be the symptom that people are most concerned about but as you get into these cases you find out that that's not what you should be focusing on. You should be focusing on the clinical picture of the patient. And once you read through these you really do get a sense of how they present and it becomes quite obvious to you.

I would be happy to go through some of the cases if this is a reasonable time.

DR. MASUR: And how often, in your analysis, are there hypersensitivity cases without rash? You want to just repeat that figure?

DR. HEATHERINGTON: It's about--I would have to go back to the bar graph--but it's about 20 percent perhaps. One thing about rashes that often it's very inconspicuous and you don't really notice it until you disrobe the patient for an examination. So, it's not what brings the patient to medical attention, it's the other symptoms.

All right. Let me actually start out with a one case we do feel is related to abacavir hypersensitivity and this is a patient who is in 3005. All of the other cases that are referred to are in the advanced disease patient populations. And all had stopped abacavir prior to their death.

Now, this is a 42-year old male who was enrolled in the 3005 study. And on the first day of treatment he reported that he had nausea and vomiting and five days later he developed fever and diarrhea. The next day he is seen at the hospital where his temperature is 39 degrees, his blood pressure is 83 over 46. He complains of headache and nausea and he has lymphadenopathy. He is diagnosed with the flu.

He goes home and the next day his temperature rises to 40 degrees centigrade or 104 degrees Fahrenheit. His nausea, vomiting and diarrhea are now worse. He develops a rash or at least he reports that he has seen a rash for the last couple of days but it's the first time that it's mentioned.

He's hospitalized and treated with fluids and antibiotics. His study medications were stopped and he improves the next day. He is discharged three days later. Shortly thereafter the abacavir was restarted and within 40 minutes he develops malaise, tingling in his lower extremities, feeling of pressure in his chest, fever, diarrhea, respiratory distress and syncope.

He called his doctor and was told to stop treatment and be seen if symptoms persist. He improves somewhat during the day but the diarrhea returned that night and he was found dead the next day.

Now, this is a case of hypersensitivity reaction and death upon rechallenge and it's a case that I mentioned before. And if you look at the particular characteristics of the patient they go as follows:

First of all, there is a constellation of symptoms. There is both constitutional symptoms, and there are symptoms related to the GI tract. Secondly, you will notice that there is an evolution of these symptoms over time and they increase in severity and they accumulate over time as well.

The rash onset is later than the other symptoms and it's not even noticed by the patient until his subsequent visit to the physician. It's almost an after-thought.

The symptoms resolve on stopping abacavir and they resolve very quickly. And finally you will notice that he has a positive rechallenge with symptoms returning within 40 minutes. And this is very typical of the abacavir hypersensitivity reaction. Unfortunately, it is a fatal case and we are fortunate that the other 29 rechallenges, which occurred for a variety of reasons, did not end up in any fatalities.

Now, let's contrast that with another case. This is a 38-year old male with AIDS. He has a CD-4 count of 99 and he initiates abacavir in combination with efavirenz, saquinavir and nelfinavir in March of 1998. One month prior to starting abacavir he had developed splenomegaly, fever and anemia for which he had an extensive workup including a hospitalization in May of 1998.

His past medical history is also notable for aortic cyanosis and he was an IV drug user. In June of 1998, approximately four months after starting his abacavir he develops shortness of breath, cough, fever, and chills. And he's taken to the emergency room where his temperature is 101.4. His blood pressure is 138 over 54 and in a previous clinic note it is reported as being 128 over 77. His respiratory rate is 46 and he's anxious, he's disoriented and there is no rash. His chest X-ray shows bilateral infiltrates, and a white blood cell count of

29,000.

His drugs were stopped but he developed third degree hard block respiratory failure and expired on the second hospital day.

Now, this case I reviewed with the physician who does not feel that it was related to abacavir. And there were some aspects of it that I think are important.

First of all, in the acute episode there is no history of a stop and rechallenge as we saw in the previous case. Secondly, if you look at the blood pressure he has a normal systolic but a decreased diastolic instead of the overall hypotension that we've seen with other rechallenges.

The low-grade fever actually had occurred prior to his even starting abacavir and the pattern of that fever had not changed on initiation of abacavir therapy. There was no rash. The time of onset is very late. Doesn't exclude the diagnosis but it clearly is unusual for the cases.

And, finally, he exhibits third degree heart block which is a characteristic which is not seen in hypersensitivity for abacavir nor is it recorded in the literature of hypersensitivity for any other drugs, at least, that I'm aware of.

So--

DR. POMERANTZ: He didn't have a postmortem examination?

DR. HEATHERINGTON: He did not have a postmortem which was unfortunate. One was actually supposed to be done and I agree with you, Roger. I think that we would have seen the answer there. I think that this is a cardiac complication from preexisting medical conditions.

Let's take a look at another case. This is a 44-year old male with AIDS, a viral load of 9,000, a CD-4 count of 61. And he initiated abacavir therapy in combination with ddI, 3TC, indinavir and nelfinavir in October of 1997.

His medical history is significant for IV drug use and hepatitis A, B and C. He developed PCP in February of 1998 and he also had a rise in viral load which led to a switch in his treatment to abacavir, d4T, ddI, hydroxyurea, saquinavir, and ritonavir in March of 1998.

A month later he developed progressive vomiting, for which he was treated with prochlorperazine and he next developed disorientation. He was admitted to the hospital at which point he was aphedral, normal-tensive, but unresponsive.

His liver function tests were quite elevated with an ALT of 2627. His total bilirubin s 4.2. And he has a serum ammonia of 174. All of his antiretroviral agents were discontinued. Despite support he later developed respiratory failure and he expired two days later.

Now, what's unusual about this case for

hypersensitivity it does have some characteristics that might on initial presentation might have you think about it, but first of all, you will notice again that this is a very late onset case. And he is afebrile. He is normo-tensive and all of the rechallenges with problems and all of the initial presentations of classic hypersensitivity with problems have had hypo-tension as part of their picture.

He has an icteric hepatitis instead of the usual anicteric hepatitis. That doesn't rule it out. In some cases in the literature of hypersensitivity to other drugs you do see an elevation of the total bilirubin but it's fairly unusual.

Also, you will notice that this patient's condition worsened and he finally expired after his medications had been stopped. And finally, there was no rash.

Now, while any single characteristic may be atypical in the presentation of abacavir hypersensitivity, all in this case really are very atypical and it makes it very difficult to hold this presentation together as a good case for hypersensitivity.

I will go through as many as you want. Just tell me to stop.

DR. MASUR: Why don't you run through each of them?

DR. HEATHERINGTON: Okay.

This is a 29-year old woman with HIV and AIDS who was diagnosed in 1992. She has a history of a pathologic rib fracture and fever for which she receives cefazolin for presumed osteomyelitis. In February of 1998, she initiated therapy with abacavir, efavirenz and nelfinavir. Two weeks later she complains of feeling ill: headache, fever, has mental status changes.

She is admitted in March 10th to rule out lymphoma. On that presentation she is cecitic, she is febrile, and she has bi-basil rales and hepatic smegaly. Her SGOT is elevated to 375 as is her SGPT to 197, and her total bilirubin is 3.6 with a direct of 2.6. Her CD-4 count is 19.

CT scan of the abdomen showed splenic infarcs, a bone scan shows multiple rib lesions and there was a presumptive diagnosis and treatment for Bartonella infection.

Two days later her SGOT and SGPT increased. She is transferred to hospice care and she expires on March 13th. This patient did have an autopsy. The examination of the liver showed central lobular necrosis but no inflammation, no ise infiltration. The spleen had infarcs. The lungs showed bronchial pneumonia with micro-colonies of organisms found on microscopic examination.

Now, this case has some characteristics that should certainly raise the question of a hypersensitivity reaction. But how the case evolves and the results of the autopsy, I think, eventually direct you away from that diagnosis.

First of all, as in the previous case the fever began before the initiation of the abacavir therapy. Secondly, she has an icteric hepatitis picture instead of the usual anicteric picture. There is no rash. And the autopsy shows the focus of an infection for which probably was involved in her ultimate demise.

DR. POMERANTZ: What was in those bone lesions?

DR. HEATHERINGTON: I don't recall the pathologic examination.

The next case is a 32-year old male with AIDS who is living in a transitional housing and nursing facility. His past medical history is very complex. It's notable for cerebral atrophy since July of 1997, and a depressive disorder with psychotic features and suicidal attempts. Chronic wasting, hepatitis B infection as well.

In January of this year, he initiated treatment with abacavir, d4T, saquinavir, and ritonavir. Nine days later he was admitted to his hospital with suicide ideation, poor appetite, poor memory, weight loss and diarrhea.

There was a confirmed diagnosis of C-dificile

diarrhea. He was treated with metronidazole and his psychiatric state was managed with sertraline and alanzapine.

In February he developed pain and tenderness at an old PICC line site. He was treated with cefazolin for presumed thrombophlebitis. However, he developed progressive diarrhea, generalized pain, insomnia, and redness at the current right PICC site, for which he was receiving TPN.

His white blood cell count, his LFTs, and his creatine are all normal. At 2:15 he is visited by a nurse who records a pulse of 140 but no palpable blood pressure. The patient had anorexia, diarrhea, and emesis. He refused hospitalization and he refused all medications and he expired the next day.

Now, this is obviously a very complicated medical history. But the story is of one of documented C-deficile infection with progressive diarrhea. The physician also notes that he received 19 different medications in the 10 days prior to his death.

There was no fever, no rash, no elevation of LFTs. Again, throughout the course of this illness the signs and symptoms were limited to the GI tract consistent with his diagnosis of C-deficile diarrhea. There was no threat of an immunologic reaction for a group of symptoms that can come

together really hold together a picture of abacavir hypersensitivity reaction.

The next case is a 32-year old male with HIV and cerebral atrophy. I'm sorry, a 31-year old male who is HIV positive since 1987. He has a history notable for MAC tuberculosis, cryptococcoses, staphaureus pneumonia and shock in July of 1997.

CNB retinitis in November of 1997. Neutropenia, pneumococcal sepsis, and he's receiving foscarnet intravenously for his CNB retinitis. His abacavir was initiated as a part of the open label program in October of 1997, along with d4T, 3TC, and nelfinavir.

In January of this year, he developed a temperature of 40 degrees centigrade, facial edema and an eruption covering his entire body and face. He is admitted to the hospital and on exam has generalized urticaria, bilateral conjunctivitis, pain and swelling in the right arm.

He developed hypertension and expired soon thereafter. But a blood culture the day before his hospitalization grew out staphylococcus aureus. Now, this case also has an initial presentation that should raise the question of abacavir hypersensitivity.

It did initiate about 10 weeks after starting abacavir which does not exclude the diagnosis of a

hypersensitivity reaction but it is later than in the typical case. However, the history of prior episodes of sepsis, the presence of a PICC line with clinical evidence of inflammation and thrombo-phlebitis and the signs and symptoms of an infection at that site, all should bring in infection as part of the differential diagnosis.

In fact, this entire clinical picture is consistent with the positive culture for staphylococcus aureus and a diagnosis of toxic shock syndrome.

The next case is a 35-year old male with AIDS who initiated abacavir in September of 1997. He added that at that time to his current regimen of zidovudine, 3TC and ritonavir. Other medications included phenobarbital for control of seizures, acyclovir, clarithomycin, trimetha-sulpha. He has a past medical history of CMV disease, seizures, deep pain thrombosis and pneumonia.

One week after starting his abacavir he develops a fever to 104 degrees Fahrenheit and he complains of headache. He is admitted. Chest X-ray and blood cultures are negative. And abacavir is discontinued.

A Galian scan reveals uptakes in his lungs. Three days later he develops seizures which are controlled but he develops seizures again the following day which leads to cardiac pulmonary arrest and death.

Now, this case because of its timing, its fever,

and its constitutional symptoms again raised the question about whether this is a hypersensitivity reaction. But abacavir was stopped very early in the presentation of this illness; despite this he progresses.

Actually despite this, he does well; it's really the seizures that occur that caused the problems. There is no other organ system involved that has been documented. And three days after stopping his abacavir he develops seizures which have not been seen with abacavir nor with any other drug that causes hypersensitivity reactions.

The death appears to be due to the cardio-pulmonary arrest which is secondary to his seizures. So, the current data does not make this a case of hypersensitivity reaction but we certainly would be agreeable to investigating this case further by the review of other primary sources such as the clinic notes.

Yes, Dr. Pomerantz?

DR. POMERANTZ: Just so I get this straight. He was a man with AIDS who was admitted to a hospital with a fever of 104, a headache and he had no MRI--

DR. MASUR: Roger, can you talk into the microphone.

DR. POMERANTZ: Yes, sorry.

I am just trying to get the clinical cases down. I know they are at various hospitals. But this is a 35-year

old man with AIDS who was admitted to the hospital with a fever of 104 and a headache and you have no documentation of an LP or a CT or an MRI?

DR. HEATHERINGTON: He had a CT which was normal not different from baseline.

DR. POMERANTZ: But he never had an LP?

DR. HEATHERINGTON: I can't recall that to be honest with you. But he was evaluated for his headache and fever and appropriately and did not have any evidence of CS infection.

DR. POMERANTZ: Okay.

DR. HAMILTON: To what were the seizures attributed prior to his admission to the hospital?

DR. HEATHERINGTON: I don't have the answer to that; it's a long-standing past medical problem that he has had.

Let's go on to the next case. This is a 25-year old female with AIDS who is receiving abacavir, ddI and nelfinavir beginning in October of 1997. Approximately two months later she is admitted to the hospital with a history of progressive fever, shortness of breath, cough and nausea. Her ABG shows a PH of 7.16 with a PC02 of 26 and a PO2 of 64. She was intubated and received ventilatory support. Treated with vancomycin, santazomine, doxycycline, pentamidine, and steroids; the latter two for presumed

pneumocystis cruniae pneumonia.

However, there was no ideology for the pneumonia found despite a bronchoscopy. The patient did improve, came off the ventilator by December 31st. She was restarted on her antiretroviral therapy while in the hospital and at the time of her discharge on abacavir therapy. She was afebrile, had no cough, no shortness of breath.

However, the patient was found dead the next day after discharge at her home. The diagnosis was pneumonia. There was no autopsy done. And the investigator recorded that the death was not related to abacavir.

Now, this case also begins with symptoms that are consistent with abacavir hypersensitivity reaction and the case against the hypersensitivity reaction is the negative rechallenge following reintroduction of abacavir while in the hospital. Nevertheless, we are willing to request additional documentation and evaluate this case in greater detail.

Now, that brings us to the end of the cases. And, again, I want to reiterate that the picture of abacavir hypersensitivity has evolved over the course of our clinical development program. And it will continue to evolve. We are committed to continuing to collect data, to work with the Food and Drug Administration and physicians to better characterize this. The primary goal is to give physicians

and patients the information that they need to incorporate abacavir safely and effectively into a treatment regimen.

DR. MASUR: Pam, other issues?

DR. DIAZ: No.

DR. MASUR: Okay.

DR. EL-SADIR: I have a couple of questions.

So, out of the 99 cases of definitive or probable hypersensitivity reactions, it sounds like you believe that there was one death.

DR. HEATHERINGTON: That's true.

DR. EL-SADIR: That was likely due to--

DR. HEATHERINGTON: That's true.

DR. EL-SADIR: Okay.

DR. HEATHERINGTON: And I should reiterate that one death where the documentation is sufficient to make that diagnosis. The other cases that I just presented have been raised by the FDA as questionable cases and rightly so. I think the analysis is as I presented will lead you away from that diagnosis but as the picture of this evolves we are certainly willing to revisit these and other cases and to expand our definition as the experience grows.

DR. EL-SADIR: Have you gone back to look at the death in general? I mean do a more like active, actually seeking of the causes of death amongst your study participants? Because clearly there are often the cause of

death is rather mysterious and people will often put down as a cause of death advanced HIV or to try to find out their unexpected death that may be related to subtle dimensions of hypersensitivity.

DR. HEATHERINGTON: Well, I think that was really the issue of these latter cases to do exactly that. And I think that is the kind of analysis that is really very helpful.

We do have a listing of deaths which I believe are in your briefing document. And they are showing the cases as listed in the expanded access program. And, again, the vast majority, as you have said, are recorded as being progression of disease or complications of HIV.

We don't have any indication by reviewing those deaths that there are other cases that we would have missed.

DR. EL-SADIR: Another question that just unrelated to the hypersensitivity reaction, of the 173 patients in your 3003 study, the adult treatment naive, how many of those had been switched to the three drug regimen at week 16?

MR. LAFON: Do we have a slide? We have a slide on this. Okay. In the two treatment groups, the abacavir treatment group and the 3TC, that opening group, 87 and 86 patients were randomized. Four patients in the abacavir group and five patients in the other group did not take

study drug. So, they were randomized but never took the study drug.

And at week 48 of treatment, 67 of the original 87 patients in the abacavir 3TC zidovudine group remain on the original abacavir 3TC zidovudine. However, only 8 patients continue to remain on 3TC zidovudine in that treatment norm.

Forty-nine subjects in the 3TC zidovudine arm switched treatment to abacavir 3TC zidovudine and an additional 8 subjects added abacavir and changed one of their nucleosides most commonly taking zidovudine out and putting d4T in. And seven patients added abacavir and at least a protease inhibitor and/or a non-nucleoside reverse transcriptase inhibitor.

Interestingly, in the patients originally randomized to abacavir, 3TC and zidovudine, only three of the patients changed their therapy from the abacavir, 3TC zidovudine treatment.

DR. MASUR: And, Steve, are we to presume that you have no hemodynamic or electronic physiologic or PFT data on patients who have possible hypersensitivity syndromes?

MR. LAFON: We have no data, no.

DR. MASUR: And any plans to look at such data prospectively?

DR. HEATHERINGTON: You raise a very good point. We've had quite a discussion among us to look at ways to

investigate hypersensitivity reactions in a number of ways. That would be one that you mentioned but in addition to that there is certainly good cause to look at metabolic and immunologic mechanisms of this reaction, as well as looking at some innovative ways to manage the hypersensitivity reaction.

But we're open to suggestions from the committee and we have engaged in discussions with experts in the field to further look at this.

DR. MASUR: Just one other question before we move on to Dr. Lipsky. Is there any evidence of lipodystrophy in patients who are on this three-drug nucleoside regimen exclusively?

DR. HEATHERINGTON: No, there's not.

DR. MASUR: And lipid abnormalities?

DR. HEATHERINGTON: Well, in the data that I presented to you the only studies in which we've seen elevation of triglycerides is in the AIDS dementia trial where there is background therapy that can include protease inhibitors and the frequency was equal in the abacavir and the control groups.

DR. MASUR: But in the other studies--

DR. HEATHERINGTON: We don't see any elevation in the mean changes over time, that's true.

DR. MASUR: Okay.

DR. LIPSKY: Thank you.

You brought up the issue of metabolism and in the background information and also what you presented, you said that the drug is metabolized by alcohol dehydrogenase and you show in the background information that it goes to the caboxolate acid. Is that by alcohol dehydrogenase or is it also this sequentially metabolized by aldehyde dehydrogenase? That would be relevant to drug interactions with disulphran but metronidazole as you had up there et cetera.

DR. YUEN: We don't have direct evidence that it goes through the aldehyde dehydrogenase although we suspect that is the case. We haven't been able to look at that intermedia from the alcohol dehydrogenase, the intermedia which we haven't found and then the next step to the caboxolate

DR. LIPSKY: It seems like that might be important information. Certainly for a disulphran interaction. Potentially for metronidazole, I noticed for one of the cases up there received that drug although that is a less certain issue with aldehyde dehydrogenates. Also, if you are making an aldehyde that is a potentially reactive compound.

Also, along the lines of metabolism you mentioned the neonates that you were doing studies. Is there

decreased glucoronization in neonates with this drug?

DR. YUEN: We have data at this time to look that we have nv hand. Those studies are underway.

DR. LIPSKY: But you are, I presume you are looking for it.

There was a statement about that you have data for continuing the drug if rash developments with good results. Could you clarify the good results or at least quantitate them?

DR. HEATHERINGTON: Right. What we have basically is through the expanded access program. We prospectively gathered data on rash and if you look at what physicians did, in those cases where there was rash alone without any other systemic symptoms, the vast majority of those cases just continued dosing with abacavir and had no difficulty.

Now, in some cases, the abacavir was discontinued but we don't have the details as to why. There may have been other reasons besides the rash.

Whereas, those cases where there were symptoms related to organ system involvement or constitutional symptoms along with the rash, the majority of those cases actually terminated dosing with abacavir.

DR. LIPSKY: And, so, the knowledge of what really happens, what percent you can continue you couldn't really say, is that right?

DR. HEATHERINGTON: Well, we actually have that slide. No, that's not the one. That's all I have. I'm sorry, we did not bring that data.

DR. LIPSKY: The other thing that impressed me the eight cases is that it looked like because you have multiple drugs and a lot going on, it looked virtually impossible to really state, I think, probably for any case, even quote, the rechallenge case, that you really knew that this was cause and effect. Can the same be said for the hypersensitivity? I mean is that clearly such a defined clinical entity that you can say it is with the drug or if you were to flash up, you know, 10 cases of what you think is clearly hypersensitivity, could someone say, well, how do you know it's not X, Y and Z drug?

DR. HEATHERINGTON: Right. Well, I think you bring up a very important point and if you look at the literature the experience of hypersensitivity to other drugs, you basically arrive at the same kinds of conclusions we have with abacavir.

The sine qua non is a rechallenge and an immediate return of symptoms and it's a rather dramatic return of symptoms in the case of abacavir. So, that is the best data to say that it is related.

Early on we actually had some patients that were rechallenged two or three times, believe it or not.

Fortunately, they did all right in the long run. But it was very clearly associated with the reintroduction of abacavir.

The probable cases you really have to take the clinical picture which you see from the definitive cases and what you know about hypersensitivity to other drugs, what's possible, what's been seen. And, again, this is, although perhaps not the same frequency, has been reported with all other classes of antiretroviral agents in the literature. And you will see a very consistent type of clinical pattern.

DR. LIPSKY: And that comes out despite--so, it's the rechallenge is basically what you're going on because--

DR. HEATHERINGTON: That's exactly true.

DR. LIPSKY: That is the main thing. And how many times has that actually been done?

DR. HEATHERINGTON: Thirty that we have presented today.

DR. LIPSKY: Thank you.

DR. MASUR: Roger?

DR. POMERANTZ: Yes. First, thanks for a nice presentation.

I have a couple of questions virologically to get off the hypersensitivity. First of all, the questions have to do with the durability and the intensity of viral immunological effects. You show all your data as undetectable, being less than 400 copies. There are now

really fairly compelling data from San Diego, Geneva Groups and others, that for durability it would be nice to see what the reanalysis of under 50 would show.

Do you have that data?

MR. LAFON: We have the data. I can speak to it, but you can put the slide up. In the 3003 trial is where we have that data in our adult trial comparing abacavir, 3TC, zidovudine to 3TC, zidovudine. We used the Roche Ultrasensitive TM assay to do those studies. And I mentioned earlier by intent to treat, 75 percent and 35 percent of the two treatment groups were less than 400 copies per ML. Using the Roche Ultrasensitive TM assay, using a cutoff of 50 copies per ML, 54 percent versus 15 percent were below 50 copies per ML.

DR. POMERANTZ: If you go to meetings whether you see the data, there is always anecdotes of people saying the triple parte inhibitors are not as intense as with a protease inhibitor. So, I would like to see some data with this compared to indinavir, 3TC, and AZT.

MR. LAFON: That is planned. We don't have that data yet.

DR. POMERANTZ: You don't?

MR. LAFON: No. The data we showed today is hot off the press. While we are doing those assays at week 16, we don't have that data to show today.

DR. POMERANTZ: Okay. Because as you probably know that is continuous rumor that goes around from anecdotes.

MR. LAFON: And it's important and I think it's something that we have built into all of our Phase III and future protocols is to use the ultrasensitive assay but we just don't have the data.

DR. POMERANTZ: Thanks.

The second question is getting to the immune parameters. You show some increases in some of your studies of CD-4 counts and I agree with what was said that the first phase is probably redistribution of memory cells of CD-45, RO positive. If you follow these patients out in most studies now for up to six months or longer, at the six-month range if you believe trans-data, that's where you start seeing the naives come back.

Do you have any data on your immune parameters at that point, with RO and RA positivity? Because again there may be a difference between them.

MR. LAFON: We have conducted a study in collaboration with Dr. Guisippe Pantaleo and he conducted a study in actually patients who were treatment naive and fairly in disease with the combination of abacavir and amprenavir and we have preliminary data looking at the immunological characteristics early on in trial. And if we

can find that, the bottom line from that is we do show both a increase in both the naive and the memory CD-4 cells. And this is after 48 weeks but as you can see it's an ongoing study. And, indeed, the number of patients fall off dramatically at the later time points.

But you see a dramatic increase in RH plus cells and also a little bit more modest increase but still an increase in RO positive cells.

DR. POMERANTZ: I remember Geppy's data. That is somewhat different from other groups because the RO, the memory is less intense than the RA.

MR. LAFON: It is important. I think, as I recall, the median CD4 cell count in these patients was 700 cells. So, fairly early in disease and there are treatment naive.

DR. POMERANTZ: Interesting.

And the final question is you didn't talk about it but it was in your briefing document, that you showed that interestingly abacavir seems to have activity in mononuclear phagocytes, monocyte macrophages and class and T cells a little like ddI, better than AZT, which is more potent in activated PMBCs. With that being said which is novel for RT inhibitors, do you have any data in thinking about or in vitro data using this with hydroxy urea both of which is why you combine hydroxy urea with ddI because they both function

well in quiescent cell types?

MR. LAFON: I will let Dr. Randall Lanier, the project virologist, address that question.

DR. LANIER: If I understand correctly your only question really is about hydroxy urea? Or do you want more detail?

DR. POMERANTZ: Yes. The point is that abacavir, if the briefing document is correct, is unique with the exception of ddI in having activity that is greater in quiescent cells than in activated cells, which is different for me. And that's the reason why ddI and hydroxy urea have been combined sort of at the beginning when you design trials because they both function in these initially quiescent cells.

Have you used that in thinking about designing protocols with abacavir and hydroxy urea and ddI because what you show in your basic material, your basic science material would suggest that you can use that to design other trials. Have you done that yet?

DR. LANIER: Right. Let me sort of go backwards. We have shown that there is greater activity both in monocyte derived macrophages with BAL and also in quiescent T-cells and these are external studies by outside investigators.

The data on hydroxy urea and abacavir is really

very preliminary. And I would hesitate to describe it because it hasn't been compared directly with ddI. I think that the levels, the effect of the ATP levels with hydroxy urea are very different than with GTP. So, we might not except as intense an effect.

DR. POMERANTZ: Thank you.

DR. MASUR: Just to clarify one thing. Steve, when you said on 3003 that it was 54 versus 15 percent or less than 50 copies, is that--at what time point?

MR. LAFON: That's at week 16 of treatment.

DR. MASUR: John?

DR. HAMILTON: I notice we are pretty seriously off schedule.

DR. MASUR: We are.

DR. HAMILTON: Will we have another chance?

DR. MASUR: After the FDA presentation we will but we would like to for the sponsor have at least the major part of the questions now.

DR. HAMILTON: Okay.

I have several questions probably for Dr. LaFon and Dr. Harrington.

They revolve around the patient population in whom we might consider using this drug. First, I had the impression from the case presentations regarding hypersensitivity, not having been given in most cases an

indication of where in the stage of their illness they were, I had the impression that some were rather early in the stages of HIV infection suggesting that patients were being aggressively treated with a variety of regimens and maybe I will just begin with that.

Am I correct in that assumption?

DR. HEATHERINGTON: No. Actually all these were very advanced disease patients. Because they were all enrolled in the expanded access orphan label program. And even the cases in the--I don't think there were any cases in time frame where they were actually started in the expanded access. So, they would have been under the more stringent criteria of open label. That is viral load greater than 30,000 and CD4 count below 100 and having failed prior therapy with at least one protease inhibitor.

So, they were all advanced disease patients which I think adds to the complexity. I think the past medical histories of the patients, as well, shows how advanced they were with a variety of histories of opportunistic infections.

DR. HAMILTON: The criteria for the 003 was they had a median CD4 count of entry of 450 or something.

DR. HEATHERINGTON: Well, I think just to clarify. The one death which was in a rechallenge was actually in the 3005 study. And as I had mentioned in the presentation that

was a CDC Class A patient. So, it was an asymptomatic patient in the randomized trial for abacavir versus indinavir in combination with AZT, 3TC. So, that patient was clearly not advanced.

The other cases that I presented were all advanced disease patients.

DR. HAMILTON: Okay. That's helpful. Thank you.

I'm trying to get at a balance between what we're expecting/hoping to gain versus the price we're having to pay for it. And if, in fact, a substantial number of patients are being enrolled in a regimen that includes this drug as well as others, with no documented clinical benefit, based on a short-term surrogate markers, we want to be pretty certain that we don't have unacceptable side effects that would more than counter-balance that.

And in that regard, it looks like there might be a comment in that. But in that regard, the comparison was made earlier that perhaps the protease inhibitor containing regimen that was studied in ACTG-320 would be an interesting and important comparison. And I don't disagree with that, but I think what is commonly seemingly over-looked to me, at least, is that the benefits that accrued in the course of that trial were statistically speaking almost completely confined to those patients with very low CD4 counts.

In spite of that fact, the principal of use of

protease inhibitors have been extended to a much broader range of individuals. And my guess would be that a comparison of, in your 003 trial, with the indinavir containing regimen, that it would not have been a very stringent comparison. Because not much happened in comparison to the other control treatment regimen.

So, maybe I will stop there and ask for comments?

MR. LAFON: Well, I specifically want to address the comment about limited or no activity in the risk-benefit discussion. We've actually conducted a large series of trials to try to tease out the activity of abacavir in patients who have previously been treated with nucleoside reverse transcriptase inhibitors. And our bottom line conclusions for those trials--I would be happy to summarize them if appropriate, although I appreciate we're running late--is that abacavir can show benefit in patients who have been previously treated with nucleoside RT inhibitors, however, it can be an attenuating response.

In general, our observation is that patients who are treated with nucleoside containing regimens, and specifically with AZT and possibly 3TC, under a less than optimal antiviral effect, so, patients are still having replicating virus, can ultimately accumulate a number of resistant mutations that can result in a virus that is resistant to abacavir and, frankly, resistant to most other

nucleoside RTs.

We have got a series of data that demonstrate that and that's not surprising. It's something that's been found for, frankly, another nucleosides or other drugs in other classes.

So, that's basically the response to that that the activity of abacavir is very clearly established in naives as well as experienced although the activity in experienced patients is attenuated.

DR. MASUR: John? Other questions?

DR. LIPSKY: Yes, but I will save it. Thanks.

DR. MASUR: All right.

Actually, it has been suggested that we take a 10-minute break now and give this side of the panel an opportunity to crystallize their questions when we get back.

So, we will take a 10-minute break.

[Recess.]

DR. MASUR: Dr. Matthews, why don't you continue?

DR. MATTHEWS: Okay.

I had one question relating to the dose response data, particularly in trial 2002. In your presentation you presented the four-week data which there was clearly no difference between the 300 and 600 milligram dose but in your briefing document at week 12 and week 24, while not statistically significant, there seem to be a probably

important divergence in viral load response and also in CD4 response on page 52.

Could you comment on that?

MR. LAFON: I would be happy to.

That study was designed so that after four weeks of treatment patients were getting an inadequate response to change therapy. And, indeed, as I showed on the slide, 25 percent of patients in both of the two high-dose arms, the 300 milligrams twice a day and the 600 milligrams twice a day, discontinued the study.

And, indeed, we continued to do real-time viral load and allow patients to drop out if they were not doing well. So, by the end of the 24 week study, only 7 patients in one arm and 6 patients in the other arm remained on study. Therefore, interpretation of those data beyond 4 weeks are somewhat complex.

We actually did a post-hoc pharmacokinetic, pharmacodynamic analysis which confirmed the results of the randomized trial in that which showed that there was essentially no difference that we could determine between the 300 milligram and the 600 milligram twice a day dose with regard to response to viral load or CD4.

However, we did show in that study and in previous studies a suggestion of more adverse events at the higher dose and it's specifically nausea. I know that was

equivocal when you looked across studies but it did suggest that the higher dose was, indeed, less tolerated than the 300 milligrams BID dose.

DR. MATTHEWS: Thanks.

And one question for Dr. Heatherington. The expanded access program, my suspicion is that most of the physicians enrolling patients in those trials were fairly experienced clinicians with HIV therapeutics. Is that correct?

DR. HEATHERINGTON: Well, in the open label program we did restrict the enrollment because remember at that time we had data on 200 patients. So, we selected, I think, 60 centers throughout the country, geographically distributed, to act as sites and we also instituted a much closer gathering of safety data.

But in the actual expanded access program, which began in March, it was wide open and anybody that felt they needed it for their patient could simply call up the 1-800-number and within the span of a week or two be able to initiate that patient.

So, there was a very wide distribution of the drug. Today, we have over 11,000 patients on it and there are several hundred different physicians that are participating.

DR. MATTHEWS: But, still, it's a lot of work to

get the patient on that and, at least in my own experience, an individual physician with a small number of patients is not terribly likely to want to go through the regulatory requirements.

So, I'm getting at this whole issue of how experienced a clinician needs to be to recognize this syndrome and also the management strategy of stopping the drug if hypersensitivity is suspected has at least one downside and that if you're falsely diagnosing hypersensitivity you may be prematurely disregarding a potentially helpful agent.

And particularly as the understanding of this syndrome has evolved over time I am just not completely comfortable that once a drug like this is released for general prescribing that the small volume provider will necessarily have the skills and clinical judgment to act in the best way possible.

DR. HEATHERINGTON: You raise a very good questions and let me answer them sequentially.

First, about the demographics of the actual enrollers. I don't have that information. I don't think we ever will as to how large their practices were among each of the prescribers in the expanded access program. But just to say that several hundred physicians have participated. That's as close as I'm going to be able to answer that

question.

Now, about the diagnosis of the hypersensitivity reaction, it's important to note that it is a clinical diagnosis. You don't need any special tools beyond what a physician would have and that is the ability to take a good history and do a physical examination. Whether or not any particular physician could recognize this any better than another, well, really the key point here is education. And we have initiated a large educational program during the expanded access program. We had teleconferences with anybody who wanted to call in and get information. There is specific written material for the patient and the physician.

And certainly, even beyond the point at which this drug would be marketed we would have a commitment to continue the educational process so that physicians are aware of the reaction, patients know what to expect and that the appropriate decisions can be made.

Now, the last part of your question was about what about preventing from premature discontinuations? In other words, having two quick a trigger finger to pull abacavir in the event of a reaction that may not be true hypersensitivity. I think the best way to answer that is twofold.

One is that in the expanded access program that has not been our experience. I showed you the numbers of

patients that were discontinuing prematurely because of adverse events or for other reasons.

Those numbers really are no different from what you have seen in other expanded access programs. So, we don't see this large-scale fear or concern in over-calling the hypersensitivity reaction.

I review each of these cases as they come through because it is a reporting requirement in the expanded access program. All suspected hypersensitivity reactions have to be reported and I do review those. I have been very impressed with the clinical acumen of the people that are at least participating in the expanded access program.

Now, the final point is well, what about physicians in practice who might not have a large component of HIV that they deal with. Again, I think it really gets back to the educational process that we need to be certain of. I speak of this frequently at investigators meetings, teleconferences and this sort of thing, and these efforts are going to continue post-marketing of this drug.

DR. MASUR: Brian?

DR. WONG: I guess I have two general questions. Dr. Heatherington, you might stay there. With respect to the hypersensitivity reaction, and I am concerned that the whole definition appears to have been or it may have been derived only from or almost only from the patients in whom

the rechallenge was positive.

And I would be curious to see a comparison of patients who were rechallenged who had a reaction compared to those who did not have a reaction and see how the clinical syndrome initially would sort out among those two groups.

DR. HEATHERINGTON: All right.

Well, I think you did see that in the tables of the charts of the clinical picture of the hypersensitivity reactions. You remember I broke those down into the definitive and the probable cases and the percentage with which each of those appeared.

DR. WONG: Were all the probable cases rechallenged and--

DR. HEATHERINGTON: No, no. None of the probable cases were rechallenged.

DR. WONG: Right. So, some people were rechallenged and had a reaction. That was 33 or--

DR. HEATHERINGTON: Right. If you were rechallenged and didn't have a reaction you're not included in that analysis.

DR. WONG: Right. But I guess I would have liked to have seen what those patients look like to help define really what the hypersensitivity syndrome is. But some of those patients may have had symptoms that could be ascribed

to hypersensitivity, right, and presumably they did. And well, I mean it's just I would have liked to have seen those data and I think it would be useful to see a comparison of the two groups. Those with suspected hypersensitivity in whom that diagnosis was confirmed by rechallenge as opposed to in whom that diagnosis was not confirmed by rechallenge.

DR. HEATHERINGTON: Right. We can do that type of analysis because again we do report all of these events and that's a worthwhile exercise that we will continue to do.

DR. WONG: And I guess my second question is really to take up someone's earlier offer. One of the statements or one of the conclusions from the pediatric trial was that response may have been diminished in heavily pre-treated children when compared to treatment of naive adults.

But we didn't really see any quantitative data on that point and I'm particularly interested in, you know, how heavily pre-treated does one have to be to have attenuated treatment, or attenuated response; how heavily pre-treated to have no response. I mean you must know these, right, or have some data on it?

MR. LAFON: Actually, we have got a short series of slides I will zip through here to try to give you a feel for that.

We have actually conducted a number of studies

that I have mentioned earlier of abacavir in combination, in treatment experienced patients. Actually we have provided data through nine studies of 1,300-plus patients in which abacavir is being studied and some of these studies are actually explained in your briefing document, and some of them are not. Indeed, some of them we don't have data on at this point.

But, looking specifically to abacavir in addition to background therapy, to try to get a feel for what abacavir does specifically in patients who have been previously treated. As I mentioned earlier, we have looked at abacavir, 3TC and zidovudine, and we wanted to specifically address patients who have been on 3TC, zidovudine for short periods of time and had abacavir work.

We have also looked at various combinations, abacavir, nelfinavir, amprenavir and efavirenz and ACG-372-B. Abacavir, efavirenz and amprenavir in specifically our salvage study, the protocol 2007. And abacavir, efavirenz, and indinavir in 368.

We knew from preclinical studies that abacavir showed only limited cross-resistance with many clinical isolates of viral isolates that were specifically resistant to other nucleosides. And compared to a wild type, a 184-V alone, which results in high-level resistance to 3TC, lesser level resistance to ddI and ddC was still sensitive to

abacavir, which is a three-fold change in IC-50.

And, indeed, we saw very similar things with the L-74-V resistance to ddI and ddC but only limited or modest resistance to abacavir. We define resistance to abacavir and this is sort of a working definition of four fold.

Specific mutations that result in zidovudine resistance either two mutations of the 41-215, or even four mutations at 67-70, 215, and 219, only resulted in modest effect upon the zidovudine activity or on the abacavir activity. However, we did note in preclinical trials that multiple mutations associated with zidovudine plus a 184 could result in abacavir resistant virus.

Our first study we attempted in a small pilot study--this is the study I was referring to in my talk--to evaluate adding abacavir to patients who have been on six to 12 months of either zidovudine, 3TC zidovudine, ddI or D4T. And abacavir was added to these patients and the medium plasma HIV-R in any of the groups were monitored. And we saw a very good response in most of the populations with one and a half to even almost two load drops in viral load when added to D4T specifically.

But, interestingly, and probably somewhat correlates with what we saw in the in vitro data, patients who had been on more than 12 months of 3TC and zidovudine, which was the requirement for this group, had only a modest

if no response at all.

Carrying this further and I showed you the 3006 data earlier. Dr. Yogev had asked about this question. Patients in our pediatric trial who had not been on 3TC, zidovudine, in the prior six months of the study, prior to the study had a very good response to abacavir, 3TC, zidovudine. Had a little bit of a rebound after two weeks but still maintained a one-log medium drop by week 24. And that was actually superior to those patients who had received zidovudine and 3TC alone.

However, patients who had received 3TC, zidovudine in the previous six months had a lesser response. We saw maybe a modest response in the abacavir, 3TC, zidovudine group by week 2. That response seemed to be lost and was no different than the 3TC, zidovudine group alone.

We wanted to carry this further to understand what was contributing to this and there was actually a large study conducted in Europe where abacavir was added to a stable background therapy in adults versus adding abacavir placebo. This was actually a large study, almost 200 patients, 185 patients. Should note that these patients were on a stable therapy and were judged to wanting to intensify therapy, did not want to add therapy. That was part of the protocol criteria.

And, indeed, the median baseline viral load in the

two treatment groups was about three-and-a-half logs. So, about 5,000 copies, relatively low viral load. This study showed that adding abacavir to their background therapy resulted in 42 percent of patients, approximately 42 percent of patients of having viral load less than 400 copies per ML, by week 16, versus only 7 percent in the placebo group.

It also showed that this phenomenon was seen regardless of whether patients with 3TC experience or 3TC naive, which suggested that 3TC alone is not contributing to attenuated response to abacavir.

Caring our observations further, I mention in the two previous trials that actually this is the 3003 study which we mentioned earlier when at 16 weeks patients were allowed to change their therapy to open label, abacavir and 3TC. So, indeed, patients on the 3TC, zidovudine group while they had an initial good response, they had a rebound in their treatment. And, indeed, most of these patients, I showed you the slide earlier, had switched to abacavir, 3TC, zidovudine. They had a concomitant drop back in their median viral load back to approaching and at the levels that were seen from the patients originally on abacavir, 3TC, and zidovudine and that response was maintained.

So, this suggested to us that while in previous trials 3TC, zidovudine pre-treatment may result in an attenuated or even no effect while abacavir, short-term

exposure to 3TC and zidovudine did not seem to affect abacavir activity. This was actually substantiated by another study that was done in Europe. This was specifically patients who, 50 patients, who have been treated with 3TC and zidovudine for 12 weeks in which then--and this was another study that was being done. And we just took the roll-over study where abacavir was added to these patients. These patients were subdivided at baseline as to whether they had the 184M or the 184V and, indeed, the patients with the 184M, 40 percent of those, were actually getting very good therapy on AZT, 3TC alone background. Indeed, 40 percent were less than 40 copies per ML.

When abacavir was added, we saw a very good response by week 8 and week 16 in these patients that these differences are not statistically significant and indicate that patients regardless of whether they have a 184M or a 184V actually have a very good response to abacavir therapy, at least, short-term, after short-term exposure to AZT and 3TC.

Briefly we have done collaborative studies in which we evaluated abacavir as part of an additional treatment regimens for patients who have already failed prior therapy. Of note are a couple of studies. One, ACTG-372-B, which I mentioned earlier, was a roll-over study of patients who had been on the ACTG-320 trial and specifically

had received indinavir, 3TC and zidovudine and were judged to have been failing that treatment regimen at the time of entering 372-B.

And in this study, patients received adefavir, efavirenz and nelfinavir. This was a factorial design. So, only half of the patients received nelfinavir. And, indeed, patients were randomized to receive either abacavir or one or two new nucleoside reverse transcriptase inhibitors that they had not been on before. We won't show the nelfinavir data but this study did show that the positive contribution of nelfinavir in this treatment regimen. And, indeed, at week 16 of treatment, 37 percent of the patients on the abacavir portion of the study and 32 percent of the patients on the new nucleoside portion of the study were below 500 copies per ML.

Now, this study was small. It was originally intended to enroll 150 patients. And it ended up only enrolling only 84. But the bottom line from this small and under-powered study was that there seemed to be no difference in the addition of either two, one or two new nucleosides or abacavir to this treatment regimen.

Finally, I mentioned earlier we conducted a study in collaboration with a number of investigators, our 2007 study, where we evaluated the combination of abacavir, efavirenz, and amprenavir in patients who had been failing

previous treatment regimens. And, indeed, this population was considered a salvage population and that all of them were nucleoside and protease inhibitor experienced and half were non-new experienced. Indeed, 72 percent of the patients in this study had already received in prior treatments 4 or 5 nucleoside RT inhibitors. And 60 percent had already received 3 or 4 protease inhibitors.

The results of this study are summarized here through week 16 of therapy and this study is important because this would represent the most optimal therapy that could possibly, we believe would possibly offer to these patients, because indeed, it represented three new medicines that none of them had received before. But then I had mentioned earlier that had received other drugs within the class of these.

And, indeed, at 16 weeks 26 percent of subjects had viral load less than 400 copies per ML. So, only a quarter of patients receiving all three of these medications in the salvage regimen reached this ideal target of less than 400 copies per ML.

This study was pre-stratified based upon baseline viral load above and below 40,000 and based upon non-nucleoside reverse transcriptase experience or naive. And, indeed, the population that did the best with 53 percent of patients being less than 400 copies per MI were those with a

low viral load, and non-nucleoside naive.

And, indeed, those that did the worst, with only 7 percent of patients being successfully treated, had high viral load, and were non-nucleoside experienced.

We've carried this on into our clinical virology program and what we have learned--and this is the results from our 3006 study that was shown earlier--is that if you look at the proportion of patients who have at least a half-log drop or have a one-log drop in viral load based upon they received abacavir, 3TC and zidovudine, or just 3TC and zidovudine in that study, patients who harbored wild-type virus at baseline or patients whose virus had only one or two nucleoside RT mutations had a very similar response to treatment with abacavir, 3TC and zidovudine, you know, in both of these tests.

And, indeed, those that just got 3TC and zidovudine, there was a little bit of a drop off. However, patients who had 3 or more mutations in their nucleoside RT gene had an attenuated response to abacavir.

We have actually looked across multiple studies and specifically at virus from patients who did not respond to abacavir as defined by less than a half-log sequence. And we looked at the relative percentage of mutations in the virus that is isolated from those patients. And what we see jumps out is that the combination of the 184 mutation and

multiple zidovudine mutations, specifically mutations at 41, and 67, to 210, 215, and 219, tend to be the predominant virus in patients who do not respond to abacavir.

Our findings, our general conclusions from this set of studies is that in vitro and clinical data indicate diminished activity of some nucleoside pre-treated subjects to abacavir. Long-term exposure to nucleoside RTs which can lead to 3 or more zidovudine mutations, with or without a 184 mutation, is clearly associated with a poor virological response. However, short-term prior therapy even to 3TC and zidovudine and a lesser number of NRTM mutations seems to be associated with a better virological response to abacavir therapy.

We, at this point, have insufficient data to compare the abacavir results to other nucleoside with RT inhibitors. We did a very robust clinical virology program that really tried to tease this out. And unfortunately, for other nucleosides that have been developed previously, there is just not as much data to be able to do some direct comparisons with these results.

We do believe that the best virological response likely is when abacavir is used in combination with multiple new antiretroviral agents. But data does suggest that abacavir provides benefit in some treatment experienced subjects.

That's sort of a fast summary of a fairly large data set we've done in treatment experienced patients.

DR. MASUR: All right.

We will take a few questions regarding this. I just warn the panel members that the likelihood of having lunch or dinner is dependent on how succinct you are.

[Laughter.]

DR. POMERANTZ: Never mind.

DR. MASUR: Go ahead, Roger.

DR. POMERANTZ: I find it very fascinating that this is--as I have seen before, abacavir looks a little bit more like a protease inhibitor needing numbers of mutations to accumulate as opposed to one fell swoop like most of the RT inhibitors.

You did bring up or you had at the bottom of the slide the 69 insertion mutation that was first shown by Yaup Gauschmidt and others that first insertion mutation that seems to be multi-drug resistant for a variety of nucleoside inhibitors. I know you haven't found it in vivo, but when you construct this in vitro, does it give resistance to--

MR. LAFON: I am going to take my swing at that and then if you need more clarity we will get Dr. Lanier up here.

A 69 insertion alone does not have an effect on abacavir. It is the 69 insertion plus the 184 mutation that

does show a resisted virus.

DR. POMERANTZ: How high?

MR. LAFON: Plus CDB mutations. That's why we need Dr. Lanier up here. So, the constellation of CDB mutations and the 69 insertion. I just misspoke. It is the 69 insertion plus the zidovudine mutations that can result in a resistant virus and how high.

DR. POMERANTZ: But you just need one zidovudine mutation and the insertion and then it's dead.

DR. LANIER: Like with what Brendon Larger and others have shown is that the 69 insertion either the SSS or the SSG, with multiple ZDB mutations, there's not a set pattern. It tends to be 41, 210, 215, and can cause multi-drug resistance across all the NRTIs.

And very similar to the 151 constellation of mutations.

DR. POMERANTZ: That holds for abacavir as well?

DR. LANIER: It does. We haven't found it in clinical trials. It's very rarely seen to date.

DR. POMERANTZ: Yes. Thanks.

DR. MASUR: Okay. Dr. Woolson?

DR. WOOLSON: Thank you.

I had several questions about each of the two studies, 3006, and 3003. And 3006, the pediatric study, as I understand it the primary influence was less 10,000 copies

at 16 weeks. I was wondering if you could briefly go over the rationale for including in the protocol patients who actually had that endpoint at randomization? You have roughly 20 percent of your sample that actually has less than 10,000 at baseline.

DR. HEATHERINGTON: Right.

At the time that we initiated that trial there was no data available on the viral load of children either on therapy. There was a little bit of data about viral load in the natural course of disease in children. That basically said it tended to be extremely high compared to adults and do not have the achievement of a set point at the usual time period thereafter.

So, we basically made the assumption that very few children would be under 10,000 even on therapy at the time. We did review a few anecdotal bits of data that were available showing exactly that. It was unusual to find a child under 10,000.

It was a matter of making the best guess that we could at the time based on very, very little data that was available.

DR. WOOLSON: A related question that has to do with the analysis of the 3006 data. You present in the briefing document we have summaries that show analyses by the actual randomization prior versus no-prior and then as

well, age. And then as well some additional analyses that were done on the basis of baseline HIV-RNA. And they would suggest that the primary benefit is in individuals who have greater than 10,000 RNA at baseline, and in individuals who have no prior ZDV/3TC therapy. And that begs the question of whether the individuals need to be in both of those categories to show a benefit? Or whether it is one of those alone. And I suspect you have done those analyses and would just like to hear any comments you have.

DR. HEATHERINGTON: Well, let me tell you about the definition of prior ZDV/3TC use. We looked only within the prior 6 months and said if you had both of those drugs in the prior 6 months you would be counted as having ZDV/3TC. You didn't have to have them concurrently. It's possible that you could have had a switch during that period of time and gotten them sequentially or whatever. So, the definition is a little bit loose in that regard. And you need to keep that in mind.

We did show, I think, Steve LaFon did show the data about that subset of patients with prior ZDV/3TC use basically showing no change in the median response but there were some patients that did develop a decline in viral load.

Does that cover your question? I'm not sure that I did. So, let me ask for a little bit of clarity on other points.

DR. WOOLSON: Is the effect you're seeing of abacavir, is it entirely in the group that has no prior ZDV/3TC and baseline RNA greater than 10,000?

MR. LAFON: Let me help to address that because we didn't look at--we looked at the--and I showed the data--as far as prior 3TC zidovudine or not, the results, the efficacy benefit of abacavir in that comparison looks to be primarily in the patients who had not been on 3TC, zidovudine. So, those on 3TC, zidovudine we showed limited response and it's a that we had gone through in this previous presentation because of the long-term potential exposure to those drugs.

As far as the less than 10,000 or greater than 10,000, that wasn't a pre-stratification, first of all, that was a post-study finding. When we looked at the proportion of patients who dropped below 10,000, indeed, those who were below 10,000 approximately 90 percent in both treatment groups stayed below 10,000 through the 16 weeks of treatment.

Now, when we looked the proportion who had dropped below 400, the other analysis was done. Indeed, the proportion of patients who dropped below 400 in the less than 10,000 group was highly in favor of the abacavir arm. But that was also the case for those above 10,000.

So, basically the cutoff 10,000 above or below had

no significant effect on the portion that dropped below 400 with the exception that patients were more likely to drop below 400 if they were below 10,000 at baseline.

DR. WOOLSON: Okay. Thank you.

Just a couple of more questions. In 3003, the adult study we have this anomalous result, the CD4, which everybody knows about. In the briefing document I didn't see any analysis that actually took a look at the joint distribution of CD4 and the HIV-RNA response. What we have is aggregate information. That is we have the CD4 changes, the group comparison, and then we have the comparable change for the percentage of individuals who are less than 400 copies of RNA. But, again, you're left then with the question that which particular individuals are these who are showing the--

MR. LAFON: We have not done an analysis looking at both endpoints together, which was suggested. So, we don't really have any clear understanding that would suggest any particular patient population or subgroup of patients would be more likely to fall in that category.

DR. WOOLSON: A question that came up actually in the slides that you had earlier today and it was a very nice presentation. It was helpful to me. But that indicates that the abacavir hypersensitivity that there were no known factors that were committed to this abacavir

hypersensitivity, however, it's defined here, but we're using your definition.

But I wondered if you could tell me what kinds of formal statistical analyses you have undertaken to try and understand and to try and identify factors across these studies that might be related to this particular endpoint?

DR. HEATHERINGTON: We haven't, except in the summary statistics that you were shown. We do not look at any actual statistical analyses to do that. I think there is just one piece of information though that is very important that I really haven't brought up yet. And that is that in the controlled clinical Phase III trials where the study assignments are blinded and no situation was in the abacavir hypersensitivity reaction diagnosed in a controlled patient. And I think that is very important because it indicates a very good separating of the abacavir hypersensitivity reactions with one exception and that is the 3005 study.

Now, hypersensitivity has documented with all other antiretrovirals and including indinavir. And, in fact, indinavir can give an identical reaction including the severe reactions on rechallenges as has been published in the literature this year.

So, we provided the ability to unblind patients if they had a diagnosed hypersensitivity reaction during that

study. And what we did was review those cases blinded, make the diagnosis, and then unblind them. And I can tell you that again this is preliminary data because it hasn't been finalized but of the 562 patients enrolled in that study, there were 17 cases of diagnosed clinically hypersensitivity reaction, 13 were in the abacavir group, and 4 were in the indinavir group.

And that's the first time we have seen it occurring in a control arm which basically is expected because it is a known reaction, at least, to some degree with indinavir.

DR. YOGEV: In the pediatric group, I have noticed that the median age was about 6 years of age. And as you know, in the pediatric they will have viral load in those less than 2 or 3. Did you sub-analyze those who really have the high, less than 3 years of age, 2 years of age?

DR. HEATHERINGTON: No, we did not do that analysis. But we do have it split up by age but not by viral load and there is no different by age group.

DR. MASUR: Other questions?

DR. HOGAN: I have several questions about the analysis of both the pediatric trial and the adult trial. It's my understanding that for the traditional application its desire is to demonstrate efficacy in the long-term and that both the pediatric trial and the adult trial would be

included in the traditional application.

One of my concerns is that the protocol for each of those calls for switching into the antiviral arm or into the ABC arm at 16 weeks. And, so, what I am wondering is how those trials can be used to demonstrate long-term efficacy if almost all the patients are switching off of the placebo arm after 16 weeks?

MR. LAFON: That's not quite accurate. That is true for the 3003 study, the abacavir, 3TC, zidovudine versus the 3TC, zidovudine in adults. Indeed, we did offer at week 16 for patients to switch to abacavir, 3TC, zidovudine, open label. And we have had discussions with the FDA about this and we have agreed that that will be a supportive study for traditional approval but will not be a pivotal trial.

In contrast, the pediatric trial, the 3006 study, remains randomized, remains blinded and patients beyond 16 weeks continue on that blinded therapy unless they meet a specific virological switch criteria. And then at which point they are allowed to use any of the study medications, plus any marketed agents to construct an appropriate switch regimen.

DR. HOGAN: I wonder if you could just review in detail those switching criteria? I think there were three that I remember.

MR. LAFON: Yes, there are. And they are different for each protocol.

This is the 3003. And for this, the first trial, the switch criteria was at week 16 and beyond and a patient has a viral load above 400 copies per ML. This is confirmed by retest. They will have met the virological switch criteria and be able to switch therapy.

In the pediatric trial beginning at week 8, any patient who had a viral load of 10,000 or above which was confirmed by a rechallenge, by retest, was considered to have met a switch criteria. And then the 3005 protocol we had the same criteria for 3003. At week 16 and beyond if anyone had a viral load of 400 copies or above and was confirmed by a retest they were considered to have met a virological failure and they could switch therapy.

DR. HOGAN: Okay. So, I guess the question is still the same and let's turn to the pediatric trial. And that is if patients are allowed to switch at some point, how exactly do you plan to adjust the analysis to show long-term efficacy because at week 24, actually in the pediatric trial after week 8, your randomization no longer holds for those week-by-week comparisons. So, what is the plan for adjustment?

MR. LAFON: The primary analysis for both the 3003 and the 3006 studies, is defined in the protocol as timed to

a virological event.

But once they've met the switch criteria, they've indeed met an endpoint. Indeed, we will also do in the analysis the proportion of patients who are below the cutoff limits defined in the protocol at week 48. For 3005, it's a different endpoint. It's the proportion of patients at week 48 in the blinded study whose viral load remains below 400 copies. So we'll, of course, do the secondary analysis, time to virological event, but the primary analysis for that study is proportion of patients less than 400 copies at week 48.

DR. HOGAN: Okay. So turning to the CD4 analysis of these data, one of the switching criteria that I read in the drug application--and correct me if I'm wrong--is that patients are also allowed to switch if their viral load--this is in the adult trial, I think. They're allowed to switch if their viral load is less than 400 copies per mL, and that is--

MR. LaFON: Yes.

DR. HOGAN: The justification given was that they were allowed to switch at that point because then they would--the ABC arm would maintain their decreased viral load. Is that correct?

MR. LaFON: In addition to the virological failure criteria defined in the protocol, we also have criteria

defined for CD4 failures and clinical events. Those would be considered failures as well and would lead to, first of all, the ability to change, to switch treatment, but also would be considered as a study endpoint.

DR. HOGAN: I think I didn't really phrase my question correctly. Let me just ask it this way: If a person meets HIV--they meet the RNA less than 400 criteria, and they're on the ZDV/3TC arm, so now they're less than 400, are they then allowed to switch after week 16 to the ABC arm?

MR. LaFON: Are you talking about the 3003 study where everyone was allowed after week 16 to change? Is that--

DR. HOGAN: I'm talking about either study.

MR. LaFON: For the pediatric trial--could you rephrase your question? Because I'm obviously having trouble following.

DR. HOGAN: Okay. Here's why I'm concerned. One of the efficacy outcomes is CD4, and there was a concern in the adult trial that CD4 was elevated in the ABC arm. And in thinking about long-term CD4, that is, beyond week 16, if anybody is allowed to switch, including those who are doing well on the placebo arm, then it becomes very difficult to figure out whether or not ABC does have a differential effect on CD4 compared to placebo, the reason being that by

allowing the good subject to switch to the ABC arm, you're actually taking the good subjects away from the placebo arm, putting them on the ABC arm, therefore bringing the CD4's perhaps closer together. So that's my concern, in essence.

MR. LaFON: Right. And obviously, as I think we had indicated earlier, 3003, the data for 3003, this is the only study where we allow patients to switch regardless of their therapy status in week 16 to open-label treatment. So the results for that study are critical for today's discussion on accelerated approval, but we've already agreed with the FDA that study, because of the issue you just raised, becomes only a supportive study for traditional approval because patients were allowed, without reaching an endpoint, to change therapies at week 16.

The other two studies we mentioned, the 3006 study and the 3005 study, remain intact as originally designed, and they should be useful for traditional approval.

DR. HOGAN: Okay. Now, I have a question about what do you do with people who drop out of the study. In the protocol application--sorry, in the NDA, it says that no data were imputed for those people who dropped out of the study. However, then there was a list of three steps that were taken to actually fill in data for people who left the study.

So what I'd like to know is if you could just,

number one, let us know if there is a protocol specified for following up people who leave the treatment. That's question one.

Question two is: If a person leaves the treatment and they can still be followed, are they included in the analysis?

And the third question is: Could you just review for us the filling-in process that's used to fill in data for those who left the study?

MR. LaFON: I'm going to address the first two, and then I'm going to ask Dr. Amy Cutrell, our project statistician, to come and address the third.

For patients who meet failure criteria or who stop taking medication, we're continuing to follow them in part of the study. The only patients that we don't follow are those who are lost to follow-up, so we cannot obviously follow them.

For our rigorous intent-to-treat analysis, a patient who discontinues from therapy, is lost to follow-up, whatever, is still included in the analysis, and that's the analysis I showed today.

Now I'l ask Dr. Cutrell to come in and talk about some--

DR. HOGAN: Can I have just one follow-up as a practical matter? What happens if a patient is lost to

follow-up? Is there a protocol for calling them or trying to get in touch? Or is it that they just miss a visit? Do you know what the protocol for getting people to stay on the study is?

MR. LaFON: We ask our study centers to be rigorous in trying to keep patients on study, but ultimately if patients are indeed lost to follow-up to the study center and they don't have contacts with them, we don't have the ability to monitor that.

DR. HOGAN: So there's no specific algorithm?

MR. LaFON: There is no specific algorithm beyond-

DR. HOGAN: Okay. And then just as a follow-up to one of your responses, you said you could follow people after they go off of the treatment, but are there data included in the analysis?

MR. LaFON: Yes, and I think I actually showed data for, for instance, 3003 where they switched. We'll continue to monitor them. And one of our analyses, our intent-to-treat where switch is included, includes those patients who have switched to treatment. We also in our most rigorous analysis, intent-to-treat, where switch equals failure, and those patients are included in the analysis, but they're included as failures.

DR. HOGAN: So somebody switches--so, actually, if more people are switching on the ZDV/3TC arm, by definition,

there's going to be more failures in that arm. Is that--because they're the--

MR. LaFON: In that analysis--and, again, the study is remaining blinded for 3006 and 3005. So while patients may be switching, they're not switching because they know what treatment they're on. It's only 3003, again, where we allow it at week 16 for patients to switch to open-label abacavir or 3TC/zidovudine.

I want to reinforce here that at the time we did that, we did not reveal to the study centers or to the patients what medication they were originally on. So they basically chose to either stay on their original randomized therapy or switch to open-label medication without knowing what they were originally randomized to.

DR. HOGAN: So is it possible just to review the filling-in criteria, how the data were filled in?

MR. LaFON: Sure.

DR. CUTRELL: Hi. The missing values, the statement that was in the briefing document that said no data imputations were made for missing values, was true for the RNA and CD4 measured values over time. For the comparison of proportions, we did construct those, including all patients randomized into the study.

As has been previously discussed, if the patient had previously dropped out, then they were included as a

failure. If they had never started treatment, they were included as a failure. If they were still on randomized treatment, however, with just missing that particular study visit, then the preceding visit week was carried forward to that point of the analysis. If that visit was also missing, then the result at that time was considered a failure.

DR. HOGAN: Okay. So there was some filling in of data. If a person missed a particular visit, then their prior visit was carried forward?

DR. CUTRELL: Yes.

DR. HOGAN: Okay. I have just two or three more questions. I know it's kind of running along, but one more about the statistical comparison in the pediatric study, and this kind of follows up Dr. Woolson's questions. That is, in the pediatric comparison, the decision was made to stratify on less than 10,000 viral load or greater than 10,000 viral load, and the comparison of proportion of children attaining less than 10,000 viral load at week 16. Is that--

MR. LaFON: No, that's not correct.

DR. HOGAN: Oh, I'm sorry.

MR. LaFON: The study was pre-stratified at entry by age and by prior 3TC/zidovudine used in the last six months. We did observe, though, in our analysis that a higher proportion of patients started in the study at less

than 10,000 than we had anticipated. So we did our first analysis that I've indicated in my discussion without accounting for baseline plasma HIV-RNA, and we had a p value at 16 weeks of 0.054.

However, we did a secondary analysis where we did indeed account for the fact that a lot of patients had already reached the endpoint before they started on the study, and that had a p value of 0.006.

DR. HOGAN: Okay. That's actually my question. So when I said stratified, I meant you stratified in the analysis, not--

MR. LaFON: We did a post hoc analysis accounting for the plasma HIV-RNA.

DR. HOGAN: I see. And, actually, what happened is that when you did your post hoc analysis, accounting for baseline HIV literally means stratifying on HIV--sorry. Accounting for baseline viral load literally means stratifying on baseline viral load and combining across those two categories because you reported the so-called Mantel-Haenszel test, which does exactly that.

Now, I don't want to get too much into details, but here's my question. If you do not adjust for baseline viral load, the comparison is not significant.

MR. LaFON: It's 0.054, so it's marginal.

DR. HOGAN: It's marginally significant. But when

you do control, all of a sudden it's highly significant. Now, the indication for stratifying from a statistical point of view is that if you stratify the analysis in the two categories, the effect that you see should be the same in the two categories. But, in fact, in one of the stratification categories, the effect of ABC on viral load is almost zero, and in the other category, it's very strong.

So my question is: How are we to interpret this analysis which on the one hand shows a marginally significant result, but then on a stratification analysis that wasn't planned shows a very significant result?

DR. CUTRELL: I think there are a few things going on to derive the p value to present such different results. It is a complicated story, and what you said is true. If you look at the patients who entered with viral load below 10,000 copies, the effect was essentially the same in the two treatment groups: 89 percent in one group versus 88 percent in the other.

If you look at the proportion of patients--at the subgroup of patients who had more than 10,000 copies, what we saw is that the effect of the abacavir through PC ZDV arm was 40 percent below 10,000 copies compared to 18 percent. This was, as has been discussed already, a post hoc finding. We were surprised by this. However, by adjusting for it in the analysis, we were still comparing all patients who

enrolled into the study. It wasn't a subgroup analysis.

We did also do those subgroup analyses where we did the test within a subgroup, and not surprisingly, there was no statistical significance in the RNA group with less than 10,000 copies at entry, while there was in the subgroup of patients with RNA greater than 10,000 copies at entry.

DR. HOGAN: Right. So my concern actually is that when you compare--when you report an adjusted analysis, you're actually reporting an analysis that you say applies to the entire population. My concern is that it really doesn't apply to the entire population. It only applies to those with RNA copies over 10,000 to start with. Now, for those under 10,000, there seems to be equal maintenance or something like that. So my only concern is really in the interpretation. I think it's--to report the analysis, the adjusted analysis, as the analysis that applies to the entire population is not quite right. That comparison, the effect is only seen in those with the RNA values over 10,000 to start with. That's my concern there.

MR. LaFON: Your statement is correct, that the one group, the group that's below 10,000, was maintained on both treatments, with approximately 90 percent in both treatment groups remaining below 10,000. And, therefore, the proportion of patients dropping below 10,000 was obviously in favor of those who were already above 10,000.

DR. HOGAN: Again, I'm talking about the interpretation of the effect, not the method. To characterize that as something that applies to the entire population is--that's what I was led to think. So the last question is just a public health kind of question. It's about the hypersensitivity. That is, a lot of HIV populations of patients are transient. Where I live in Rhode Island, there's a lot of HIV-positive women, especially in the prisons, and also HIV-positive men. So I'm just concerned from a general public health perspective about the effect of using ABC therapy in transient populations where, if this is out for a while, it might not be known what their prior history is and whether or not the detrimental effect of rechallenge is something that you see right after the treatment was stopped or is something that could possibly be seen weeks or months down the line.

DR. HETHERINGTON: I'll start with the last question first. I don't have any data to know about how far out you could go and still see the effects on rechallenge. Most of these are rechallenged within a few days or a couple of weeks. So there just isn't in any information on that.

With regard to the applicability of abacavir to the populations that you identified, I think that's a good topic for discussion really among the committee to consider that type of strategy as to how best to implement it given

that. But you also have to understand that hypersensitivity reactions or, in fact, allergic reactions to medications among all HIV patients is considerably higher than that of the general population. You're all aware of the data with sulfa, atovaquone, but also even pencillins have a higher rate of reactions among these patients.

So it's not a question that is limited to just this particular drug, but I think it applies across the board to all medications and how you manage that particular type of patient population you describe.

DR. HOGAN: Thank you very much.

DR. BERTINO: You had about--I think I heard you say you have over 10,000 patients in your expanded access program now?

MR. LaFON: We have in excess of 11,000 as of today. Not all of those were submitted as part of the NDA.

DR. BERTINO: Do you have any data on human teratogenicity of this drug?

MR. LaFON: We'll have to ask Dr. Zeman. Dr. Zeman is the project toxicologist. Dr. Zeman, can you come to the microphone?

DR. ZEMAN: The complete toxicology package, (?)-ivity and the peri-, post-natal, two species, rabbits and rats, and finding what we have only in the rats is in the highest level where we had maternal toxicity at 1,000 mg/kg.

There were no findings in rabbits.

DR. BERTINO: Any of the women in the expanded access program, have they become pregnant? And do you have data on the outcome?

MR. LaFON: We're aware of two women in clinical trials who have become pregnant on trial, on studies. One woman discontinued therapy. Another one actually had a selective abortion. So we have no data to follow up on those.

DR. BERTINO: For the hypersensitivity reaction, to return to that, in your 11,000-plus people in the expanded access program, I assume in your clinical trials you probably collect data on compliance by either looking at blister packs, pill counts, or some other commonly used method. But in the expanded access program, I would guess that data is not collected.

Do we have any idea whether people are starting and stopping the drug and, in fact, hypersensitizing themselves?

DR. HETHERINGTON: We don't have any data on that, but I will say there's no evidence that intermittent administration increases the risk for the reaction, and that's true for other medications as well. There's very little known about the determinants of hypersensitivity reactions to drugs. There are hypothetical mechanisms of

action, but there really is no data that shows that starting/stopping would increase your likelihood of such a reaction over time, with any drug that I'm aware of.

DR. BERTINO: In terms of the mechanism, is GW looking at lymphocytes or, you know, getting serum to look at TNF and things like that?

DR. HETHERINGTON: Right. There are a number of discussions we're having with experts in the field about looking at the mechanisms of this, and it sounds like you're pretty familiar with the area and realize that it is a very difficult problem to sort out.

DR. BERTINO: Okay. Moving on to some of the pharmacology and the dynamics, could you folks review in terms of sex differences the pharmacokinetics, the efficacy, and the toxicity of this agent?

MR. LaFON: Dr. Jeff Yuen will come up to address that question. While he is, let me make note that we will be monitoring patients who receive abacavir as part of the marketed program of our pregnancy register program like we do with all of our other products.

DR. YUEN: Let me ask you to repeat your question.

DR. BERTINO: Sure. Could you please review, in terms of men versus women, the difference on pharmacokinetics, clinical efficacy in terms of reduction in viral load, and side effects?

DR. YUEN: I can address the first issue, and then I think Mr. LaFon and Dr. Hetherington will address the next two issues.

We have looked at the effect of gender in terms of pharmacokinetics, and it's an ongoing trial. Let me see if I can find the slide. Yes, BE-21. These are relatively small numbers. In the 2001 trial, we observed a difference in women who had--and these women had higher exposures than men, even correcting for weight. They had a Cmax that was 30 percent higher and an AUC that was 54 percent higher. Given the safety profile for abacavir, we do not feel that these differences are clinically significant.

Aside from that, we have also done a population pharmacokinetic analysis, and, again, small numbers of women. In that analysis, we did not see a significant difference. And I think overall at this point the data we have is somewhat equivocal.

We are continuing to look at gender differences in our Phase 3 trials where we have collected population kinetic analysis, and we are continuing to do that.

MR. LaFON: Just to add to that, we have done a crawl study analysis of our Phase 2-3 studies, looking for efficacy differences between gender or safety differences, and the bottom line, while there is no--the numbers are small, there doesn't appear to be any difference between

gender with regard to either efficacy or safety parameters measured.

DR. BERTINO: Is that because the numbers are small or is that--

MR. LaFON: The numbers are relatively small. Approximately 15 percent of the enrolled Phase 2-3 studies were women, so we're talking about, you know, a relatively small number to look through this kind of detailed analysis.

DR. BERTINO: The same question for ethnic differences.

MR. LaFON: And the same response. We did an analysis, again, across major ethnic classes for both efficacy and safety parameters and did not see any difference in either of those parameters measured.

DR. MASUR: Okay. Jeff?

MR. BLOOM: Thanks, Henry.

I'd like to pick up on a point that Dr. Hamilton raised, which I think is an important point, which is the difference between looking at these studies and the reality of how this will actually be used once it's released in the marketplace and people are actually using it. And one of the things that you pointed out is that abacavir is most likely to be used with multiple new antiretroviral agents, and it's actually a two-part question. Has abacavir been looked at in use with ddI/d4T or in combination with d4T/3TC

in naive patients?

MR. LaFON: We have done a number of studies, as I indicated, Phase 2 and Phase 3, and, of course, in our expanded access program as well, in which abacavir has been combined with all the marketed agents. Specifically for naive patients, the combinations you're requesting we have not studied as yet. As I mentioned earlier, we did study abacavir in combination with all the protease inhibitors, and in our treatment experienced protocol, actually several of them, combinations of abacavir with other nucleosides have been evaluated. As a matter of fact, I showed some of the data earlier from the treatment experienced group.

MR. BLOOM: But not specifically with those combinations, because you're looking--you're trying--your approval is based on a three-nucleoside regimen, and when you look at the data, ddI d4T has sustained effect in a two-nuc regimen, but AZT/3TC does not. So it seems like you may have shortchanged yourself on this drug without--not looking at Ziagen in combination, with that combination as a triple-nuc regimen.

MR. LaFON: I do agree that abacavir in combination with other nucleosides may be appropriate and is worthy of study. I think that would be an appropriate study to do. We chose abacavir to be combined with 3TC and zidovudine because 3TC and zidovudine have actually been

shown to have clinical benefit, both in adults through the Ceasar study and in children through ACTG 300. So it seemed like an appropriate dual-combination nucleoside to be evaluated in adding abacavir to it, and indeed many other recently developed products, including indinavir, nelfinavir and sisteva (ph), have all done studies in combination primarily with 3TC and zidovudine.

MR. BLOOM: I was looking at particularly the fact that there's a large experience AZT/3TC population out there already. If the benefit to abacavir is going to be with using it with multiple new drug regimens, it would be particularly helpful to have that information, I think.

The other point is a more broad point, and that is, the basis of accelerated approval is that it's supposed to show a meaningful therapeutic benefit over existing therapies. What do you feel you've shown today that shows that this has a meaningful therapeutic benefit over existing therapies that we currently have?

MR. LaFON: Okay. I'd be happy to address that. We mentioned earlier abacavir represents a product that can be administered as a convenient dose. It's actually one pill administered twice a day, with or without food. It has a potent intrinsic antiviral activity, a good safety profile. The most significant safety issue is hypersensitivity, which has been well characterized.

I think we've demonstrated, at least in preliminary results from a short-term trial, a 24-week trial, that the combination of abacavir with 3TC and zidovudine is comparable to that of indinavir and 3TC and zidovudine. So it represents a potential alternative for patients who, because of their choice or because of the feeling that they do not want to take protease inhibitors or can't take protease inhibitors, that this regimen could be used. It does represent potentially, with the administration of the Combivir tablet, administering two pills twice a day. We think that's a major advance.

The other thing we've shown is that this drug does have activity in patients who have previously been treated with nucleosides and so, therefore, can serve as a component for a multi-drug switch regimen in combination with protease inhibitors and/or non-nucleosides for that patient population.

MR. BLOOM: I think that's my particular concern, that you brought up the Combivir tablet, and I think that, you know, from the patient perspective, obviously we know that the first choice people are going to make is probably their best choice, a successful reduction in viral load plus it affects their subsequent choices. And I guess, you know, my concern would be that Combivir and abacavir are being marketed together without really understanding abacavir with

ddI/d4T or d4T/3TC. Are we actually doing the patients a disservice by putting it out there without having that information already?

MR. LaFON: As I indicated, we have data in combinations with other nucleosides. Our major emphasis was with combination of 3TC and zidovudine for the reasons I explained. Conducting additional studies in combination with other nucleosides seems like an appropriate approach.

MR. BLOOM: So there's none planned in your follow-ups currently?

MR. LaFON: Well, actually, I should say that, you know, we've talked about the studies initially identified for traditional approval. But we have either internal studies or collaborative studies amounting now to over--in the hundreds with abacavir, and indeed, abacavir is being evaluated in these studies, either conducted by us or collaborative with groups like the ACTG, with the ICC, with other companies, with other investigators, evaluating abacavir in pretty much any combination you can imagine.

MR. BLOOM: Thanks, Henry. I'll leave the rest of it to the discussion.

DR. MASUR: Just a couple of follow-up points. Obviously we need to focus on the data that's been submitted, and whereas, there may be advantages of abacavir containing combinations for salvage, I guess in terms of

just talking about an accelerated approval, that's not really data that's been submitted here for our consideration.

MR. LaFON: Every study that we have reviewed today has been submitted to the agency. Many of the latter studies, especially the study in my supplemental talk, have been submitted relatively recently and are results from ongoing studies. So, indeed, the studies that we summarized in the beginning of the talk, the Phase 3 trials, are the basis from our submission for this product.

DR. MASUR: The other issue in terms of safety is I think Brian made a very good point that there is a patient population out there that appears to be particularly well defined. It would be nice to have more data on that patient population.

We have in the past dealt with this problem before. There have been other drugs that there's been great concern about because of the issue of how you would identify patients and how you would communicate to the physician population and the patient population when to avoid the drug or when to discontinue it.

Could you be a little more specific about if this drug obtained accelerated approval how you would reach the patient and physician community and what specifically you would say?

DR. HETHERINGTON: Well, all of that is in discussion with the FDA, but we have proposed a patient package insert which would provide information to the patient at the time that they receive an abacavir prescription. In addition to that, there are obviously educational initiatives that we are considering for the education of physicians, particularly about hypersensitivity but about the total safety profile of abacavir. And many of these issues I think we've talked about before in the course of today's discussion.

DR. MASUR: Since we're running behind schedule, as has been pointed out, I think what we're going to do is we will have the open public hearing now. We'll then break for lunch, and then we'll have the FDA presentation and then addition discussion.

For the open public hearing, the first comment will be made by Gerald Breitman.

MR. BREITMAN: I am Gerald Breitman, and I do live at 15 Industry(?) Drive in Durham, North Carolina, and I am a long-term survivor of HIV. I appreciate the opportunity to address this group and for the opportunity to do it now rather than later in the day.

Although it's impossible for me to be certain, I believe that I was infected with this virus in 1981 when I contracted hepatitis C. What is certain is that my life

partner, Stephen Dorn Breitman, was diagnosed HIV-positive in January of 1987. And while I didn't confirm my HIV diagnosis until September of 1989, I assume that I was positive as of 1987, if not before.

Since that time, I have taken virtually every antiretroviral drug that's been made available, approved by the FDA, with the exception of ddI. Beginning with Retrovir or AZT or zidovudine, or any one of the many ways it's characterized, these drugs have truly been life-savers to me. They have kept me alive and kept me in relatively good health until early 1995 when my health began to decline rather rapidly. And despite trying a variety of dual-therapy regimens, it was clear then that my immune system was failing very rapidly.

In May of 1996, I began triple combination therapy with retrovir, efavir, and Crixivan, and that combination was highly effective. It reduced my viral load from just over 191,000 copies per mL to undetectable levels. Fourteen months later, however, despite consuming about five liters of water a day, I had two bouts of kidney stones within a one-week period. That clearly ended my Crixivan part of my combination.

Since then I have taken virtually every protease inhibitor that's available with my most recent combination being that of Combivir, Norvir, and Invirase. And I took

that from July of 1997 until about six weeks ago, despite the fact that it had major side effects that were almost incapacitating. And it was six weeks ago that I substituted Ziagen for the Norvir and Invirase protease inhibitors that I was taking. And I am indeed a part of the Glaxo Wellcome expanded access program.

When I did that, I had truly nearly reached the end of my ability to tolerate the daily nausea that I experienced, the numbness of mouth, numbness of tongue, lips, my teeth actually hurt every day just--if you've ever been coming down with a cold and the cold gets into your teeth, well, that's how my teeth felt every day. And after 14 months of that, I had really gotten to the point where I just didn't think I could continue that regimen, although I didn't seem to have any other place to go.

I've been aware of Ziagen since it was known as 1592, and I was concerned early on that when it became available, there will be very little data available to me or my physician about its possible efficacy in patients like myself. So I must tell you that I am indeed very grateful that my doctor had data available on Ziagen as applied to experienced patients to help us support the decision for a need to replace my protease inhibitors with this new drug. And I truly believe that it's important for FDA to continue to encourage companies to gather this kind of data so that

those of us who are long-term survivors can have some benefit and know how to use these drugs.

Simply stated, the Combivir-Ziagen regimen has indeed given me back my life, and I don't mean to be over-dramatic. But it has just really changed the way I am able to live. And while my HIV-related fatigue remains unchanged, the fact is that no drug regimen has addressed either the HIV-related fatigue I've had for years now, nor has it addressed the malaise that generally accompanies at least my manifestation of this virus.

But the Combivir-Ziagen regimen has eliminated the nausea and the other side effects that were just so absolutely devastating for 14 months. It's also had a dramatic effect on the number of drugs I take every day. Until six weeks ago, I was taking 28 tablets or capsules every day. My current regimen is 11 tablets. That is a dramatic decrease in the number of drugs.

It's at least my view that there are far too few drugs available to help manage those of us who are living with HIV, and, of course, I think Ziagen is an important drug to add to the prescribing armamentarium.

I guess it goes without saying that it's incredibly important to me that Ziagen be approved for marketing so that I can be assured of continuous availability of this drug that has so significantly improved

my quality of life.

I do thank you for your attention and for your interest and for allowing me to address this hearing, and I would be delighted to answer any questions that you might have.

DR. MASUR: Thank you, Mr. Breitman. We appreciate your comments.

If the committee has no questions, we appreciate your perspective. We'll now move on to Mike Donnelly from Act Up Golden Gate.

MR. DONNELLY: Yes. Hi, I'm Mike Donnelly from Act Up Golden Gate. We don't take any drug company money, so we don't have any conflict of interest.

I guess I've been pretty disappointed today in the data that was presented. We don't have any data on the durability of this combination. To compare it to the 16-week data with indinavir seems premature. We have concerns about the hypersensitivity issue and the education of the physicians and the community about this drug. And I think most of all we're concerned about the price of this drug, although I know this hearing has nothing to do with price. But the company seems to be, from what we hear, going to price the same as a protease inhibitor, and that seems to be unacceptable.

To say AZT, 3TC, plus abacavir is as good as AZT,

3TC, and a protease inhibitor is premature, and to price it in the same range is outrageous. And our greatest hope for the drug is that this would be helping patients with more experience, drug experience, and the data doesn't show that this drug is that much better either. So although Act Up Golden Gate supports the approval of the drug eventually, I'm not sure there's compelling evidence that was presented today for an accelerated approval of this drug. But we do support the drug, and hopefully they will give us some more data with other drugs from other companies, not just their own. It seems that abacavir, AZT, 3TC, all owned by Glaxo Wellcome, was a convenient drug combination to test, and unfortunately, they haven't looked at the real-world issues, and ignored the real-world use of the drugs.

Thanks.

DR. MASUR: Thank you for your perspective.

The last comment of the open public hearing will be from Jules Levin from New York.

MR. LEVIN: Hi. My name is Jules Levin, and I'm the executive director of NATAP in New York City, the National AIDS Treatment Advocacy Project. I really wasn't sure if there was a need for me to speak, but now I think there is.

Let me say that I support the approval of this drug. I think it's an important addition to the drugs

available for people with HIV for the naive as well as the experienced population, although I do have some concerns about the hypersensitivity, which needs to be addressed. And I hope that maybe we can come out of here today with a commitment from the company to do a specific amount of education for doctors--not just for doctors but for patients. I think that it's very important for the patient population to be able to recognize and know what to do if they begin to experience this side effect, not just the doctors, because I think it was brought out by the panel, which is really very true, that maybe a lot of doctors who are unable or incapable of recognizing hypersensitivity. So it's really important to have the patient population to be able to do it.

Let me say I think that the data is obvious and compelling that this is a potent drug. In the naive population, I think if you look, Glaxo has done extensive cross-resistance research with this drug, probably more to date before accelerated approval than any other drug we've seen so far. And I haven't really heard the data discussed in depth. I assume that it's in your booklet. I don't know if it is available for you to have read prior to today. And obviously some people will not respond. If you look at some of the data that was presented at the last retrovirus conference, some people will not respond. Extensive cross-

resistance data showed that if you had greater than eight-fold phenotypic resistance at baseline, you would not respond to abacavir. People with less than eight-fold phenotypic resistance at baseline had either intermediate response or better response. With up to four-fold resistance at baseline, they had a full response, maybe a little less with intermediate response. So it's kind of been mixed in the experienced population.

I have HIV. I think that this drug should be available for me if I need to switch to a new regimen. And I think that people who have experience with nucleosides need to be able to consider this option.

Now, in the naive population, I think the data is fairly clear. With the Crixivan study and with the Margaret Fischel (ph) data at 16 or 24 weeks, it's kind of obvious. This is accelerated approval, not full approval. I don't remember if we had more than 24 weeks data for ritonavir and for indinavir. In fact, if you'll recall--some of you are new faces here, but Crixivan just got by, 13 to 5 on the vote. Ritonavir was voted down on the first go-round. I'd like you to remember that. Also, you should remember that the Antiviral Committee at the time didn't want to approve viral load testing.

I think what we do need is a little more research, and that's what accelerated approval is for and that's what

post-approval studies are for. We need a little more research, and I'd like to hear a commitment from the company, and I'd like to have the panel help the community in this respect. We need more studies characterizing the use of this drug in the nucleoside experienced population. We need to learn more about sequencing, using abacavir first, and then using abacavir after d4T and/or ddI and see what happens. And we need to further characterize how to sequence this drug in the full complex of all the nucleoside regimens.

I think that asking the community speak before the FDA presentation is inappropriate because we're unable to address the FDA's observations here. I think that it sells us short, and it makes me wonder why you did that.

I think it's very important that we have pediatrics data here. I think for the first time we have some clinical data on pediatrics. I think that that's really very important and that this should set a tone for future applications for other drugs that we want clinical data here for pediatrics. And I think lastly what I'm going to say is just to briefly address the pricing issue.

I think that the pricing issue for this drug and for efavirenz, frankly, and for future drugs to come in the near future is much more complicated than is being proposed by many people speaking to this issue. And I think that we

have to be very careful how we address this issue, and I think some of the conversations are very dangerous for people with HIV who want drug development in the pipeline and want drug companies to stay in the business of developing new drugs for HIV. That does not mean that I don't want fair pricing. I want fair pricing, and I think that this issue is very complicated and cannot be addressed in one quick sound bit. So maybe what's needed here is a more comprehensive examination of the whole situation, but it's much more complicated than is being presented to the public. And since there's some press here today, that's one reason I'm mentioning this. I think that the press--I would hope that the press would be a little more responsible than they've shown me in the past in addressing these kind of issues.

There's one other thing I want to mention which the press also mishandled out of Geneva, was that NATAP in New York City does a lot of treatment education in the community amongst all different types of populations. We do treatment education of 20 ASOs throughout New York City and upstate and Long Island. And what came out of Geneva was the scare about side effects with protease inhibitors, which have not been characterized well. We still don't understand the cause, and we don't understand the mechanism, and we don't understand the association with therapy or with PIs

very much. Everyone has an opinion, but it needs a lot of work.

But what happened was because of how the press handled it was a lot of people--it's not uncommon now in New York City--and I have firsthand experience with this when I go out and do treatment education. People have stopped therapy and they were doing well. They don't want to start therapy, a lot of people, and it's all to do because of the headlines that came out of Geneva and the scares. And a lot of people--this goes back to the population who didn't want to take AZT because they thought it killed people, and then when the data looked good with PIs and people were getting healthier, people started trying therapies. And now in a sense I feel like we're back to square one with people going off therapy and not want to start therapy. And it's really a problem in New York City. It really hinders treatment education a lot, and I really don't know what to do about it.

So what I want to say is I think that the addition of this drug as a treatment option is really important for people who may not want to take a protease inhibitor. They may not want to take a non-nucleoside, and that's an important contribution also. This gives us an extra option in addition to having a non-nucleoside option. This gives those people an option. A triple-nucleoside option for a

certain population has a certain appeal, and I think you cannot overlook that in the full scheme of things. And plus the pill count makes a big difference. In the community, people have to live with taking these drugs. The pill count is really important.

So I hope you will consider these things. Thank you.

DR. MASUR: We appreciate the comments from the community. Let me respond to two things that Mr. Levin asked.

The reason that we had the open public hearing now is twofold: One is the administrative policy is that when we publish that the open public hearing will be at a certain time, we try to have it as close to that time as possible. The other is that one of the three speakers had to leave before noon.

If any of the individuals who spoke at the open public hearing feel compelled to speak again after the FDA presentation, we would be happy to give those individuals that opportunity if you indicate that to Rhonda Stover.

Again, I apologize for being off schedule. There are obviously a lot of issues here. We appreciate the sponsor's willingness to address them with the available data.

At this point we will take a break until 1:15. At

1:15 the FDA will make their presentation, and we'll try to move as expeditiously as possible to finish relatively on time.

[Luncheon recess.]

AFTERNOON SESSION

[1:17 p.m.]

DR. MASUR: Again, I apologize for being off schedule. There are a number of committee members who have early planes to catch, so we are going to try to move expeditiously. And as I mentioned before, if any of the three people who made statements at the open public hearing wants to have a follow-up after the agency presentation, if they'll let Rhonda Stover know, we'd be happy to provide them that opportunity.

So we'll now move on to the FDA presentation that will be introduced by Dr. Cvetkovich.

DR. CVETKOVICH: I should have coached you. I'm sorry.

Good afternoon. Welcome back. I'm Therese Cvetkovich, the medical reviewer for this application, NDA 20-977 for abacavir sulfate. The FDA presentation will focus on our analysis of the efficacy and safety of abacavir for the treatment of HIV infection.

I will provide an overview of the clinical trials that we plan to discuss. Then Dr. Michael Elashoff, who is the statistical reviewer for this application, will provide the agency's analysis of efficacy. Following that, I will present our clinical conclusions regarding efficacy, and then I will review our safety concerns, focusing on the

hypersensitivity reactions associated with abacavir treatment, and then will close by summarizing some of the important issues that review of this application has raised.

The applicant has reviewed for you the studies included in the abacavir development program. Our presentation will focus on those studies that we believe provide comparative data by which we evaluate the efficacy and safety of abacavir.

First are the two studies, 3006 and 3003, providing efficacy and safety data to support abacavir for the treatment of HIV infection. At the time of submission, the NDA contained complete 16-week efficacy and safety data from these two principal controlled trials; 24-week efficacy and a more limited safety data was submitted early in August. Study 3003 was conducted in 164 treatment-naive adults, and Study 3006 was conducted in 205 treatment experienced pediatric patients. Both studies were randomized, placebo-control comparisons to the triple-nucleoside combination of abacavir plus zidovudine and lamivudine, to the double-nucleoside combination of zidovudine and lamivudine.

The next study is the AIDS dementia study, 3001. This study evaluated the addition of abacavir to background therapy in about 100 patients with AIDS dementia and compared the background therapy--and compared the results of

neuropsychological testing after 12 weeks of treatment. This study utilized a higher dose, 600 mg b.i.d., than that proposed for marketing, providing useful safety data at this higher dose as well as providing comparative safety data in advanced patients. While the expanded access study, 3008, initiated in July of 1997, does not provide a treatment comparison, it contributes much to our safety review due to its large size.

Because of our concern about the adequacy of the submitted data to the NDA to support approval, we requested that the applicant provide any further viral load and CD4 data for our review. Although we did not expect to have further data prior to this Advisory Committee meeting, preliminary viral RNA and CD4 results from Study 3005 were provided in mid-October. This ongoing study is being conducted in 552 treatment-naive adults. It is a 48-week equivalent study, equivalence design being conducted by the applicant to support traditional approval.

Other studies for which the applicant has recently submitted executive summaries include Study 3002, which evaluated the addition of abacavir or placebo to background therapy, as well as ACTG Studies 368 and 372. All these studies were conducted in treatment experienced patients.

Dr. Mike Elashoff will now provide the analysis of efficacy.

DR. ELASHOFF: I'm Dr. Mike Elashoff, the statistical reviewer for the application. My talk will focus on the two principal studies from the NDA for the HIV indication. I will then briefly discuss some of the other studies that may offer some additional efficacy information. These include two studies submitted with the NDA: the AIDS dementia study, 3001, and the expanded access study, 3008, that collected RNA and CD4 information as secondary endpoints.

In addition, we recently received summaries of three additional studies--3005, ACTG 372, and ACTG 368--that may provide further insight into the efficacy of abacavir.

The first study I will discuss is the pediatric study, 3006. This compared the triple-nucleoside combination abacavir, ZDV, 3TC versus the dual-nucleoside combination ZDV, 3TC, with approximately 100 per group. This study is ongoing, and we have data from the first 24 weeks of the study in this application.

Subjects start with a median RNA of 4.6 log copies or approximately 40,000 copies. This is very similar to the median RNA from the adult study, which I will be discussing next. Baseline CD4 was approximately 700 cells. Subjects ranged from six months to 13 years of age, and all were treatment experienced. The median duration of prior ZDV was approximately one year, and the median duration of prior 3TC

was approximately 3 months. Prior ddI or d4T use was less common.

This figure shows the result for the protocol primary endpoint of RNA less than 10,000 copies. Shown at the bottom are the number of subjects with data at each time point. The analysis follows the division's convention of treating dropouts as failures in the primary analysis. In the figure, note that approximately 20 percent of subjects started at less than 10,000 copies. The response on each arm peaked after about two to four weeks, with subsequently lower response rates. While the numeric advantage at 16 weeks approach significance, much of this advantage was lost post 16 weeks.

Ten thousand copies is not the typical RNA cut point in HIV trials. So even though this primary endpoint did not identify a meaningful difference between the arms, we were interested in the results for the standard 400-copy analysis.

This figure shows the results for the secondary endpoint of the percent less than 400 copies. Again, we can see a response peaking around weeks 2 to 4 and a steady decline after that time. There was a statistically significant difference between the arms at weeks 16 and 24, the time points of primary interest. However, recall that the median RNA baseline was relatively low, 40,000 copies,

and 20 percent of subjects started below 10,000 copies. Thus, the response rates, 12 percent on the abacavir arm and 2 percent on the control arm, are quite low. Further, examination of the subjects who were responders at week 16 revealed that about half of them had started below 1,000 copies at baseline.

This figure shows the CD4 results from the pediatric study. Complete CD4 results were only available up through week 16 in contrast to the HIV-RNA data. Findings for CD4 were similar to HIV-RNA, namely, numeric but not significant advantages were seen for the abacavir arm.

This slide summarizes the efficacy results for the pediatric study. In the protocol primary endpoint of 10,000 copies, there was a numeric advantage for the abacavir arm at week 16. But after 16 weeks, there was little difference between the arms. In any case, 10,000 copies is not considered to be the current goal of therapy. The results at 400 copies were statistically significant, but the response rates were quite low, and while not significant, the CD4 results did favor the abacavir arm.

I'll now turn to the adult naive study, 3003. This compared the same treatment combinations as the pediatric study. While designed as a 48-week study, after 16 weeks subjects were given the option of receiving open-

label triple therapy. Most subjects availed themselves of this option. In particular, this included subjects from both arms who were being successfully suppressed to below 400 RNA copies. Since most subjects in the two arms were receiving the same treatment after 16 weeks, we will be focusing on the 16-week time point as the most important for assessing relative efficacy.

The median baseline RNA was about 35,000 copies, similar to the pediatric study, and the median baseline CD4 was 450 cells, making this a relatively healthy population at baseline.

Here are the percent of subjects who are below 400 copies at each time point. There is a clear and significant difference between the curves at the end of the 16-week comparative portion of the study.

This figure shows the median change from baseline CD4 over time. In contrast to the HIV-RNA results, however, the CD4 changes from baseline looked better on the control arm. This was true at each time point, and notably at the primary analysis time point of 16 weeks. The p value for the CD4 difference was 0.089 using the Wilcoxon test.

Note that missing data was roughly uniform between the groups, with 13 subjects on the control arm and 9 subjects on the abacavir arm having missing CD4 measurements at week 16. I will discuss the potential impact of missing

data shortly.

So we have a situation where the two markers of interest, HIV-RNA and CD4, may be indicating different things. The RNA response was superior in the abacavir arm while the CD4 response was inferior.

We felt that the CD4 finding merited further analysis. Since this was the first Phase 3 study in the naive population, the difference, 67 cells, is sizable, and the virologic and immunologic treatment effects were inconsistent. We identified several possible avenues to investigate this unexpected CD4 finding. We conducted analyses to rule out possible alternative explanations such as baseline imbalances or the possibility that a particular subset of patients might be driving the results. We also looked at two related immunologic measures and at the potential impact of missing data.

The first baseline factor we examined was the one used to stratify the study. There were three strata of baseline RNA: less than 10,000 copies, between 10,000 and 100,000 copies, and greater than 100,000 copies. You can see that as you move from the low baseline RNA values to the high baseline RNA values, CD4 responses increase in both groups. However, the difference between the groups was essentially constant across each of the three strata. Similar analyses subset the results by baseline CD4, gender,

and race, as seen in the next figure.

This figure shows the median change in CD4 at 16 weeks. The first set of bars shows the table from the last slide graphically. In addition, results were stratified by baseline CD4 above or below the median by gender and by race. We can see that the effect on CD4 was not confined to any particular subgroup and that the difference between the treatment arms was fairly consistent across all analyses.

The efficacy database included total lymphocyte count, so we looked at the change over 16 weeks for that variable as an exploratory analysis. Note that these are medians in the table so that the median CD4 and median non-CD4 will not necessarily add to the median total. In this analysis, we see a consistently lower change on the abacavir arm compared to control for each of the markers.

As noted before, missing data was roughly uniform between the groups, with 13 subjects on the control arm and 9 subjects on the abacavir arm having missing CD4 measurements at week 16. To investigate the potential impact these missing values may have had, we looked at the last CD4 measurement prior to week 16 for the subjects who had dropped out. You can see that subjects with missing 16-week CD4 data, this slide here, tended to have smaller increases than those with observed data, minus 19 compared to 47, and 46 compared to 113 However, again, we see that

the differential between the arms is fairly similar.

Combining the observed data with the last value from the dropouts, we can see that the dropouts only had a modest impact on the results. Also notable was that there seemed to be an imbalance in the number of subjects whose CD4 had fallen below baseline, 31 percent on the abacavir arm compared to 19 percent on the control arm.

In summary, each of the CD4 analyses we conducted were consistent with the original CD4 finding. Thus, while there is a positive impact on RNA relative to control, the evidence pointed to a negative impact on CD4 relative to control for this study. However, each is an important surrogate marker.

The accelerated approval regulations state that results from adequate and well-controlled studies must demonstrate an effect on surrogate endpoints sufficient to conclude that the drug is reasonably likely to provide a meaningful therapeutic benefit over existing therapies. In this study, we are left with no clear message about the relative efficacy of the two arms based upon the combined effect of the surrogate markers, HIV-RNA and CD4.

After identifying the concerns raised by Study 3003, we asked the applicant for an early look at the results from their ongoing equivalence study, 3005. This study was deemed to be relevant to potentially address the

concerns because it studied the same arm, abacavir/ZDT/3TC, again, in treatment naive adults. The applicant agreed to put together this first look at the results of Study 3005.

Recently, the applicant provided a summary report and a preliminary data set. This data set includes CD4 and HIV-RNA data, but does not yet include many things that are necessary for a complete analysis, such as demographic variables, center, and concomitant antiretroviral therapy. Given this, we must not view the preliminary analysis of 3005 as definitive.

Although many subjects had data to week 20 or 24, due to the preliminary nature of the data it was not possible to determine the disposition of all patients past 16 weeks. For this reason, we will focus on the week 16 results.

This slide summarizes the preliminary look at the blinded efficacy data. There is a relatively high rate of dropouts and/or missing data, 24 percent through week 16. This is especially relevant in an equivalence study where the impact of missing data may be to make the response rates more similar.

At 16 weeks, the two arms have relatively similar HIV-RNA responses, 59 percent and 61 percent. The response rates in an as-treated analysis were 62 percent and 65 percent, respectively. These numbers may differ from the

applicant's numbers since failures are treated--since dropouts are treated as failures in this analysis. It's important to note that based on our recent experience it has been difficult to differentiate regimens based on 16-week data from an equivalent study.

The CD4 responses were more similar than in the previous study, which provides some reassurance since this is an active controlled study. There are significant caveats, however. The impact of the high dropout rate on the assessment of equivalence will need to be further investigated. Additionally, at this time, the study is ongoing and blinded, and the database does not contain crucial variables. Firm conclusions will await the formal analysis of this study.

I'll now briefly discuss several other studies. Each of these studies were conducted in treatment experienced adults. The studies varied in how HIV-RNA and CD4 were analyzed, and for several studies, we do not yet have full study reports for complete data sets. So we'll just show one slide for each study and summarize the primary analyses.

Study 3001 was designed to test the effect of abacavir on AIDS dementia. Ninety-nine patients were randomized to add either abacavir or placebo over their existing antiretroviral treatment. Most subjects were

taking two or three additional antiretroviral drugs in addition to the study therapy. As the applicant has mentioned, no effect was seen on the primary dementia endpoints. In addition, there was no significant effect seen on either HIV-RNA--minus 0.01 log change on abacavir, minus 0.09 change on placebo--or on CD4--a change of minus 1 cells on abacavir, plus 49 on placebo.

The ACTG 372 is a small equivalence study in treatment experienced subjects. It compares abacavir to the investigator's choice of other nucleosides, each arm in combination with efavirenz and nelfinavir. The study primary endpoint was composed of virologic failure and/or treatment discontinuation. In the 16-week analysis, no difference was seen in the percent of subjects reaching that failure endpoint: 67 percent failure versus 70 percent failure. However, due to the small sample size and consequent wide confidence intervals, this study will not be helpful for assessing equivalence.

The ACTG also looked at the secondary endpoint of virologic failure by 16 weeks, 46 percent failure on the abacavir arm compared to 30 percent failure on the nucleoside arm. Again, these results are not likely to support equivalence. Week 16 mean CD4 and CD8 changes were also evaluated.

ACTG 368 is our first look in a large study at

abacavir in a combination other than with ZDV/3TC. This is a placebo-controlled study of abacavir, indinavir, and efavirenz versus indinavir and efavirenz. The study design and sample size are comparable to the principal studies from this application. The preliminary ACTG analysis identified no difference between the abacavir- and placebo-containing arms for the proportion reaching the failure endpoint at week 16, 27 percent versus 31 percent, p value 0.43. There was also no difference identified for CD4, 59 cells versus 60 cells.

Study 3008 was the expanded access study. This study has a single arm, abacavir plus at least one new antiretroviral drug to which the patient had not been previously exposed. The majority of subjects received abacavir plus two new antiretroviral drugs. Efficacy data was available from the first 200 subjects who enrolled. Of these, 16 subjects had a greater than one log drop in HIV-RNA and 8 subjects achieved RNA less than 400 copies. CD4 results were not reported in the study summary.

In summary, Study 3003 provided evidence for a significant effect on HIV-RNA in the naive population. However, we are left with uncertainty regarding the CD4 response, in particular, the potential for a negative effect on CD4. A formal analysis upon completion of the ongoing equivalence study, 3005, may provide additional insight into

this assessment of efficacy for this population.

Studies 3006, 3001, and ACTG 368 were placebo-controlled studies in treatment experienced subjects. These studies found that while a numeric advantage for abacavir was noted in some studies at some time points, overall they failed to show significant effect on either HIV-RNA or on CD4.

I'll now turn the podium back to Dr. Cvetkovich who will provide the clinical commentary.

DR. CVETKOVICH: Thank you.

Dr. Elashoff has provided the review of the outcomes and some of the limitations of the various clinical studies evaluating abacavir for the treatment of HIV infection. In my presentation, I would like to first place those results into a clinical perspective. Then I will present the safety issues raised by our review of the safety database, and finally will close with a presentation of some of the issues raised by review of this application.

To summarize the three studies just presented, the short-term surrogate marker results of the pediatric study in treatment experienced subjects demonstrated only limited efficacy in this population. The protocol-defined endpoint of 10,000 copies of viral RNA is of little clinical relevance because of what we know about the goals of treatment, which is to achieve the lowest degree of viral

replication possible. We believe that the low rate of response found in this study is likely to be related to the prolonged duration of prior nucleoside treatment experienced by subjects entering a study. However, too few subjects with lesser durations of nucleoside experience entered the study to be able to make any statement about the duration of prior nucleoside exposure that may predict a lack of benefit of abacavir.

A clear antiviral effect was demonstrated by the viral load response seen in the adult naive study, 3003. Viral load reduction demonstrates a direct antiviral effect and, if durable, may be associated with clinical benefit. For the reasons outlined by Dr. Jolson, we would find similar 24-week comparative results more compelling. However, patient switching to open-label treatment does not allow for meaningful comparisons beyond the 16-week time point.

This outcome supports the antiviral effect of abacavir for the treatment of HIV infections in treatment naive patients. With the clear-cut viral RNA results from Study 3003, it has been somewhat difficult to evaluate the implications of the CD4 results. Our advice to sponsors developing clinical trials of antiretroviral agents has been that, in addition to the primary endpoint of viral load reduction, we expect CD4 results to be supportive of the

antiviral effect, that is, both markers should go in the same direction.

In the adult naive study, a CD4 response was seen, but the consistently smaller changes in the abacavir group when compared to the dual-nucleoside therapy were of potential concern. As Dr. Elashoff as shown, it did not appear that any patient characteristics within the study seemed to be driving these results.

While recognizing the limitations of animal data as well as their application to human studies, it should be noted that neither bone marrow toxicity nor lymphocytotoxic effects have been identified in the preclinical animal data. Though few of the Phase 1 or 2 studies provided comparative data, we have not identified diminished CD4 responses in patients treated with abacavir in the smaller Phase 1 and 2 trials, nor were the rates of anemia or neutropenia noted to be inconsistent with those seen in the population study.

Therefore, while evidence of toxicity in the animal data or in previous trials was not seen, we felt that this outcome could be best addressed by data from a similar population receiving the same treatment combination. Given the outcome of the pediatrics trial, we believed further supportive evidence of antiviral efficacy would also be of interest.

Our review of the preliminary data submitted from

Study 3005 indicates that striking differences between the two active treatment arms were not seen for either the virologic effects or the CD4 response. While the reasonable CD4 response found in this study is reassuring, we recognize that these are preliminary results from a single study that will require confirmation and that results from the completion of this and other studies will provide the wider experience required to more adequately address questions about CD4 responses.

The results of a number of studies as indicated on the slide in treatment experienced patients suggest that in patients who have experienced previous nucleoside therapy, we have seen very little response to abacavir-containing regimens. The data we have evaluated do not allow for a conclusion to be drawn about the duration of previous therapy that might predict this lack of response.

We believe it is important to acknowledge the applicant's efforts in developing abacavir for the pediatric population. It is notable that the second study submitted to the abacavir IND was a single-dose pharmacokinetic study in pediatrics. Given the medical need for antiretroviral agents for HIV-infected children, we believe it reasonable to proceed with the early development of a pediatric formulation.

Importantly, the applicant followed through with

their commitment to pediatrics and conducted one of their Phase 3 studies of abacavir in the pediatric population. We believe that this study contributes much to the NDA. Just as efficacy results in HIV-infected adults apply to children, likewise we conclude that these results in pediatrics apply to adults. The apparent lack of a clinically meaningful effect in these heavily pretreated children can reasonably be generalized in the adult population for extensively nucleoside analogue experienced and is, in fact, supported by other studies in adults and children.

In addition, this study demonstrates that it is feasible to conduct Phase 3 studies in the HIV-infected pediatric population, and we encourage other sponsors and applicants to view this approach as one that the agency regards favorably.

The 12-week results from the study in subjects with AIDS dementia did not support efficacy for this indication, and the applicant has not sought an indication.

We believe that studies of resistance have implications for both safety and efficacy. I would like to review our conclusions about the resistance studies submitted to the abacavir NDA.

The applicant has submitted results of both preclinical and clinical virologic studies evaluating the

development of resistance to abacavir. We have drawn the following conclusions regarding these data:

First, the mutations detected in cell cultures were also observed in HIV isolates from abacavir-treated patients.

Second, that the multiple reverse transcriptase mutations detected in nucleoside inhibitor experienced patients' isolates may affect abacavir efficacy.

And, finally, that the correlation of a particular mutation or mutations with the loss of abacavir activity has not been established.

The results of several Phase 1 and 2 studies laid the groundwork for the clinical observation that nucleoside experienced patients may be unlikely to respond to abacavir. However, at this time we do not have adequate data derived from clinical isolates with which to make clinical correlations.

DR. CVETKOVICH: I would now like to turn to our review of the safety database. Our review of the safety profile of abacavir will address stats, hypersensitivity, other clinical adverse events, and laboratory abnormalities associated with abacavir treatment.

As of the cutoff date in July 1998, the applicant reports that approximately 7,900 patients are included in the safety database for deaths and serious adverse events,

and that 149 deaths have occurred among all subjects in studies of abacavir. The majority of the deaths have occurred in the expanded access study; in the rest, 14 deaths have occurred in the Phase II and III studies.

While no imbalances in deaths between treatment arms in these studies were noted, the numbers are too small to evaluate either the benefits of treatment or risk from adverse events. With the exceptions of deaths potentially related to hypersensitivity that I will discuss, these deaths have been primarily related to the subjects' underlying HIV infection.

The most serious adverse event that has been associated with abacavir treatment has been a hypersensitivity reaction. These reactions were noted early in the development of abacavir. Though the constellation of symptoms associated with this reaction appear recognizable, considerable overlap with multiple common syndromes in HIV-infected patients will be evident.

The most common presentation of abacavir hypersensitivity reactions have included the symptoms of fever, rash, malaise, and GI symptoms such as nausea and vomiting. Myalgia, arthralgia, and paresthesia are also reported, but somewhat less commonly. If the reaction is not recognized and dosing continues, symptoms both accumulate and worsen. More severe reactions have included

anaphylaxis, hypotension, respiratory symptoms, liver failure, and renal failure.

Soon after these reactions were identified, it became apparent that re-challenge was associated with the rapid return of symptoms, and that the symptoms after re-challenge were much more severe. While the majority of reactions occur early in therapy, it should be noted that some have occurred after many months of treatment.

Laboratory abnormalities associated with these reactions have included increased liver function tests, elevations of creatine phosphokinase and serum creatinine, as well as neutropenia and lymphopenia.

I will now present two cases taken from the serious adverse event case narratives that represent fairly typical hypersensitivity reactions. The first case is of a 42-year-old white male who has a history of rash allergies to sulfa and nevirapine. He was treated with abacavir, 300 milligrams b.i.d.

Five days after initiating study treatment, the patient developed symptoms of upper respiratory infection and fever. Abacavir was temporarily interrupted and the event resolved over five days. When abacavir was restarted, the following day he developed fever and rash. One day later he was hospitalized when he was noted to be weak, lethargic, and febrile to 102 degrees.

On admission to the hospital, he was hypotensive and had a low urinary output. Subsequently he developed renal failure and progressive respiratory failure. The event was diagnosed as anaphylaxis. Laboratory tests performed at admission revealed an elevated creatine phosphokinase. Abacavir was discontinued and he was treated with intravenous vasopressors and required intubation. The respiratory distress resolved over five days, and the acute renal failure and elevated CPK level resolved over three weeks.

Case two: This 43-year-old white male had a history of Pneumocystis pneumonia and previous hepatitis B infection. He was treated with abacavir, 300 milligrams b.i.d. Concurrent medications included delavirdine, trimethoprim sulfa, fluconazole, azithromycin, diazepam, alprazolam, and amitriptyline.

Two weeks after initiating study treatment, he was hospitalized when he developed a fever of 105 degrees, nausea, diarrhea, weakness, and abnormal liver function tests. Abacavir was interrupted, along with delavirdine and most of his other medications. His condition gradually improved, and the fever resolved over a four-day period.

He was discharged from the hospital and resumed use of all medications except delavirdine and abacavir. One week later he was re-challenged with one dose of abacavir.

Approximately one hour after re-challenge, he developed hypotension, nausea, vomiting, and a generalized pruritic erythematous rash. His condition continued to deteriorate and he subsequently presented in the emergency room with a blood pressure of 60/40. On evaluation, azotemia, hepatitis, and hyperkalemia were also detected.

Abacavir was discontinued and the patient's condition was stabilized in the medical intensive care with dopamine therapy and aggressive intravenous hydration, diphenhydramine, and steroids. The patient was diagnosed with a probable severe allergic drug reaction which resolved over eight days.

These cases illustrate the potential difficulty in making the initial diagnosis, the severity of the reactions, increased severity after re-challenge, as well as the potential reversibility of the events.

To date, the applicant has reported that approximately 3 percent of patients in clinical trials of abacavir have been recognized to develop these reactions. Due to the nature of the safety reporting, at this time we do not have complete access to the safety database used by the applicant to define the incidence of hypersensitivity reactions. Therefore, we have been unable to verify the incidence reported by the applicant. In addition, we are unable to identify potentially important risk factors such

as association of these reactions with gender, race, degree of immunosuppression, or other important medical history.

As indicated in the applicant's presentation, we have identified eight cases of deaths that we view as potentially associated with hypersensitivity reactions. These cases were identified from our review of all the serious adverse event case narratives submitted to the NDA and safety updates. We included a death as potentially associated by virtue of either the identification of characteristic signs, symptoms, and clinical course, or investigator designation of the death as a potential case of hypersensitivity. Six of these deaths took place in patients enrolled in Study 3008, the expanded access program. Two of the deaths occurred after re-challenge.

We believe that identification of these potentially related deaths are useful in demonstrating the uncertainties in attribution while underscoring the potential severity of outcomes.

When increased severity of these reactions upon re-challenge was detected in October of 1997, investigators were informed about the importance of avoiding re-challenge. Wallet cards were provided to subjects in abacavir studies that described the common symptoms of hypersensitivity related to abacavir treatment, instructions for seeking care, and the potential for fatal reactions. In addition,

the agency requested increased reporting of these events and that all potential cases of hypersensitivity be reported as serious adverse events. As the review progresses, we are working with the applicant to explore ways to effectively disseminate this important safety information to patients and practitioners.

Other adverse events more frequently associated with abacavir treatment in the Phase III trials have included nausea and vomiting, headache, and malaise or fatigue. The majority of these reports have been Grade 1 or 2, and few of the events have resulted in treatment discontinuation.

In all three Phase III studies, mild elevations of blood glucose were more frequently in subjects on abacavir-containing arms. Increased ALT, CPK, or triglyceride levels were associated with abacavir arms, each one of them in one of the Phase III studies.

It should be noted that distinguishing adverse events associated with abacavir therapy in these studies is complicated by the use in combination of abacavir with other nucleoside analogs, as well as the comparison to nucleoside analogs.

Now I would like to summarize our conclusions about the safety and efficacy of abacavir. A hypersensitivity reaction to abacavir was identified in

clinical trials as the most serious adverse event associated with its use. Because it is impossible to predict the occurrence of this reaction, and because prompt recognition and discontinuation of abacavir are of paramount importance to patient outcome, it will require a major commitment by the applicant to disseminate this safety information to the community of providers and patients. How this is accomplished will be critical for the safe use of this product.

The long-term adverse event profile of abacavir remains to be determined. In the short term, it appears that the surrogate marker changes seen in the clinical trials that we have presented support the antiviral efficacy of abacavir. Long-term efficacy, that is, durability of the antiviral response or effect on clinical outcomes, is unknown.

This afternoon, in addition to your thoughts on the safety and efficacy of abacavir for the treatment of patients with HIV infection, we will ask for your advice on some of the following unresolved issues: the triple nucleoside combination; the risk/benefit ratio of abacavir in clinical use; the overlap in toxicity profile with other antiretroviral agents; as well as the adequacy of the applicant's traditional approval proposal.

Given the agents currently available to treat HIV

infection, we recognize that it is not always possible to achieve the goals of providing potent combinations that utilize more than one molecular target and mechanism of action, as well as having toxicity profiles and resistance patterns that do not overlap. However, it is not clear whether the combination of three nucleoside analogs represents appropriate therapy, and if so, for what population this would represent a reasonable combination.

How this agent will be utilized in clinical practice of course is yet to be determined. We have to date very little information on its use in combinations other that with zidovudine and lamivudine. In addition, we do not know what the implications for future treatment with lamivudine and didanosine will be, given the known overlapping resistance patterns with abacavir. It appears that treatment-experienced patients have very limited responses to abacavir, though this is the group for whom new agents are particularly needed. And, finally, the balance of risk versus benefit, given what is known about hypersensitivity to abacavir, is not known.

As a practical issue, the management of patients who developed rash while being treated with combinations of antiretroviral agents, each of which may cause rash, is also of interest. It seems unlikely that a rash associated with hypersensitivity to abacavir and a rash associated with

other antiretroviral agents will be easily distinguished, though the outcomes for each of these may be quite different.

And, finally, the results of adequate and well-controlled studies confirming clinical benefit are required for traditional approval. The division recommends that the applicant have at least two adequate and well-controlled studies that will provide 48-week durability data underway at the time of accelerated approval.

Given these requirements, we are concerned about the adequacy of the applicant's proposal for traditional approval. The adult/naive study, 3003, because the majority of subjects on the comparator arm switched to open label therapy after 16 weeks, will not provide 48-week durability data. In the pediatric study, because a very low response rate at 24 weeks has already been identified, it does not seem likely that this study will provide 48-week results supportive of the durability of effect.

Therefore, we can identify a single study, the adult equivalence trial, 3005, that appears likely to provide controlled, blinded durability results, and so have recommended that the applicant consider initiation of another study to support traditional approval.

In conclusion, we appreciate the opportunity to provide our perspective on this application. We believe

that open discussion of these issues will be useful to both the applicant and to us. We look forward to your comments and your recommendations. Thanks.

DR. MASUR: Thank you. While you're at the podium, are there questions from committee members or advisors on the agency presentation?

Dr. Kweder, do you have any comments for Professor Jolson? Jim?

DR. LIPSKY: I'm just slightly confused. On the summary slide when you talked about, you know, the safety and efficacy, about the sixth one back, I guess, from the end, you said short-term surrogate marker changes support antiviral efficacy, yet it seemed to be the flavor of the earlier part of the talk that you were saying that that wasn't the case. Would you clarify? The statistical analysis was giving a strong overtone that you weren't supporting efficacy on the surrogate markers, and your concluding side said yes. Which is it?

DR. CVETKOVICH: I think that, you know, the discussion reflects what we have gone through in trying to figure out what the CD4 results from 3003 meant, and we did spend quite a bit of time trying to tease this out. And I think our conclusion was that we really needed more data to come to any conclusion, and that we felt somewhat reassured, not completely but somewhat reassured, after we saw the

results of 3005.

So I think that the presentation probably reflected our concern, particularly given the fact that for quite some time we had no other data to look at, and that the results of 3005 really have only been very recently received. So in a way it's a work in progress, and our thoughts are certainly--we're certainly open to your thoughts on this whole issue.

DR. LIPSKY: Okay.

DR. MASUR: Dr. Elashoff?

DR. ELASHOFF: Yes. I think in naive, the naive population, there was antiviral activity as evidenced by HIV RNA. However, the net efficacy is pretty hard to determine, since CD4 and RNA are both surrogate markers, and how you weigh those, I'm not quite sure. I think it was pretty clear in treatment-experienced patients, from all of the studies we looked at, there was consistently no effect.

DR. MASUR: I guess one of the issues, I guess this wouldn't have come to a committee presentation if this were all completely straightforward.

Let me ask one procedural issue of Dr. Jolson. One of the first questions that we will get to has to do with whether or not the data are sufficient to support accelerated approval, and yet there are a variety of criteria that have been described for accelerated approval.

One is that there be sufficient studies in place for traditional approval.

If a committee member were not convinced that there was more than one study in place that would provide such data, can the committee vote in favor of approval, or would there have to be a study already underway?

DR. JOLSON: Well, I think that there's some flexibility there. In the past we've heard from this committee a strong mandate that there be two adequate and well-controlled studies, reasonably likely to demonstrate clinical benefit, that are already approved at the time that a product is approved. And that has been in the past because of concern that once a product is approved, it may be less enticing for patients to enroll in the study if the product is readily available. That was, at least initially, historically the concern.

I think for this particular committee, if you felt that on balance that you were in favor of approval, but felt that the traditional approval package was less than adequate, that you could provide a recommendation for--that the sponsor conduct an additional study, and you could additionally use it as an opportunity to say what other questions could an additional study answer that you feel aren't addressed in the current package.

DR. YOGEV: Just maybe comment about the 10,000

viral load that it seems like that you don't like. This number is coming from other pediatric studies that suggested that less than 10,000 within about four and a half years, and a good average age was about three and a half years, it's a good surrogate marker for death.

And the ACTG, pediatric ACTG chose that as another marker, because we were quite impressed on the variation that we see just here between viral load and the CD4, and just hope you will support what I am saying, because I'm not sure I'm citing it right, that 65 percent of predictability is for the viral load and about 35 is for the CD4, a one log reduction in viral load and I think 7 percentage of the CD4. So you have already another study which is showing PI even, that there is some discrepancy between those, and we started using those as a parameter, that maybe the 10,000, if we have a change in CD4, would be unacceptable like study 338 and so forth, suggests why that 10,000 came around.

DR. MASUR: Again, we're going to go around and take questions. These are some procedural issues we're addressing to Dr. Jolson et al.

DR. EL-SADR: Another question is, what about accelerated approval, and I thought that for accelerated approval the requirements are for two studies with--two controlled studies, right? Sixteen-week data with potential for 24-week data, correct?

DR. JOLSON: Well, the standard of evidence for accelerated approval and traditional approval are really the same. In other words, there needs to be substantial evidence from adequate and well-controlled studies that the drug is reasonably likely to have the effect that is claimed.

The only distinction is that for accelerated approval the endpoints can be based on changes in surrogate markers that are reasonably likely to predict clinical benefit. And the way that the regulation has most recently been implemented is with either 16 or 24 weeks of surrogate marker data and with a follow-up application for traditional approval that had previously been based on clinical endpoint studies when those were feasible, and is now and in the foreseeable future would be based on 48-week demonstration of viral suppression, durability of response.

So the standard of evidence is the same, that the evidence needs to come from at least two adequate and well-controlled studies. It's just that the surety of the endpoints is somewhat different.

In terms of the distinction between 16 and 24 weeks, previously the division has told the sponsor that they could submit their application based on 16 weeks of data, with the understanding that 24 weeks would be submitted sometime during the review cycle, sometime during

the six-month review period. And that's what the sponsor has done in this case. Additionally, other data has been provided because it was felt that the two studies alone still raised significant issues and didn't provide, alone, compelling evidence of efficacy.

In the future we will probably ask the sponsors, when they submit their initial applications, to provide us initially with a minimum of 24 weeks of data, because of the difficulties in trying to interpret shorter-term viral suppression and differences between treatment groups.

DR. MASUR: Let me ask you one other procedural issue that I think has probably been an issue for many of the committee members. When there were inquiries about how--about patients, I think that in some ways the patients who had died, the details could have been more substantial in terms of what was known and what was not known.

In terms of, at least from my personal perspective, when we inquired about what the efforts were going to be to educate consumers and physicians, the plan was quite general and vague. Now, again, it may be that that's, in this kind of hearing, all there was time for. Are we to presume that this will be the subject of much more detailed negotiation as to what that will be? Or I wonder if it would be useful to have some more concrete comments from the sponsor about what exactly they plan to do other

than "educate" the patients and physicians.

DR. HETHERINGTON: Give me a second to turn this on here, get rewired.

Thanks for the opportunity to add some more clarity to the question. We recognize, by the way, that this is one of the specific questions that's going to be asked to the committee, but just to give you some basic ideas, some of the activities around hypersensitivity reactions in clinical trials are actually quite extensive.

For instance, it has been our policy for over a year and a half now that at every scientific meeting when a presentation on abacavir is given, that there is a discussion about hypersensitivity and it is related to the study at the time. We have also done letters to physicians. We have done interviews with not just newspapers but community newsletter writers in the activist community that have been very helpful in disseminating information. We also have put out letters to physicians concerning it, and updated our investigators brochure.

Now the kinds of things, the kinds of activities after approval that would be appropriate, first of all in the labeling discussions with the agency we have proposed a physician package insert with a boxed warning at the very beginning to describe the hypersensitivity reaction and a rather extensive description of the syndrome further on in

the package insert, but there is the information right up front to at least direct the physician to additional information.

Secondly, we have proposed a patient package insert with a tear-off card which would summarize the reaction the patient could carry with them, and this is really a follow-on to what we have used in the expanded access program. I notice Dr. Matthews has his yellow card with him. It has been very useful. It basically provides information on one side for the patient, information for a physician, so that a patient on one of our studies, if they happen to go to a clinic or emergency room, would produce the card and give somebody who is not familiar with the experimental protocol at least some background information and a way to get in contact with somebody, as well.

Other kinds of items that could be done, first of all, simply a web site showing the FDA-approved labeling and whatever agreed-upon wording for hypersensitivity could be included. Letters to physicians could continue, including those directed specifically to emergency room physicians, general practitioners, or physicians who might not be in the mode of keeping up to date with all the fast-moving pace of the HIV treatment world.

We already have a 24-hour 1-800 number which is a medical information line. It is being used now in expanded

access, and it's available of course post-approval for all products that are marketed by Glaxo Wellcome. We also propose educational programs in conjunction with the patient community to continue our dialogue with them to help disseminate the word to patients, because I think it's critical that patients understand the potential for this reaction right up front.

A patient instructional brochure has been actually proposed and actually sketched up, although we don't have comments back that I'm aware of from the appropriate body with in the FDA to make comments on that, but that is in the words.

And, finally, we could propose continuing medical education programs in the treatment of HIV that would include specific verbiage and information about the hypersensitivity reaction, including illustrative cases like the ones that I presented earlier and that Dr. Cvetkovich presented later on as well.

But these are the kinds of activities that certainly can be done and that Glaxo Wellcome would commit to. It certainly is in everybody's interest that the information is disseminated and that an accurate picture of hypersensitivity is known to all physicians out there. And obviously that means that we have an obligation to continue collecting the data and to update that information to

physicians as it becomes available, because it is a very changing clinical picture which is dependent upon the body of evidence that we do collect.

DR. MASUR: Just while you're up there, I don't think any of us minimize the amount of effort and imagination it takes to come up with an effective program. But one further issue is, obviously many of these programs are logical, do you have any plans to look at the efficacy of the programs to see whether you're reaching your target audiences and whether they understand the information that's being provided?

DR. HETHERINGTON: Right. I think that's an important part. You're basically talking about verification of the penetration of the educational initiatives, and that's something that we can certainly incorporate. I think that would be very useful.

DR. MASUR: While Dr. Hetherington is up here, do we have any other questions for him?

DR. YOGEV: What part of your education is to the emergency room? See, everything here is between the patient and the doctor who is giving it, but unfortunately others are also going to see them in terms of the emergency room, other physicians, and is there any special program for them?

DR. HETHERINGTON: Well, I did mention, Dr. Yoga, we have letters to physicians specifically directed at

emergency room physicians, as well as the patient tear-off sheet so that a patient has something with them they can carry into the emergency room when they are seen, or an urgent care center, or if they're outside at another city and seeing a physician that's never seen them before and may not be familiar with the care of HIV patients.

So, yes, that is I think the important part, and I think that also ties back to Dr. Masur's question about being able to verify the penetration of the educational initiatives that we know and have a gauge of how well we're doing.

DR. MASUR: Okay. John?

DR. HAMILTON: In these days of surrogate marker endpoints, I think it's well not to lose track of what it is we're trying to accomplish here, and obviously I'm referring to clinical events that attend these treatments, and to some extent those are reflected in the adverse event rates and so on. There are some, I think, softer measures and then some extremely hard measures that we try not to reach, actually, but inevitably these things do happen.

So I have actually contributed my share to this surrogate marker epidemic, but I wonder if the company, I wonder if the company, the sponsor, has made any effort to assess any of these softer endpoints? We heard some impassioned testimony today from Mr. Breitman and others as

to the benefits of this particular drug, tangible things on their life. It would seem that this would be an important measure to keep track of, at the very least, and should not necessarily I think impede the science that the sponsor has pushed forward.

So I guess my question is, are there in fact any measures of, let's call it quality of life, for lack of a better term, on these patients who are enrolled in these clinical trials?

MR. LA FON: I assume this is on? That's a very appropriate question, and let me just review some of our thoughts along those lines.

First of all, we understand or at least believe that the issue of traditional clinical endpoint trials in today's era of antiretroviral therapy and changing therapy in response to specific surrogate markers has become a very difficult issue in the traditional of ages ago. Now mortality trials are probably a thing of the past, or at least become a very difficult program.

We have attempted, and I think we mentioned it specifically around the AIDS dementia study and our study in pediatrics, to try to monitor some other clinical events. Unfortunately, in our AIDS dementia study we were not able to demonstrate any efficacy in that population, probably we believe the result of the fact that most of those patients

indeed were harboring resistant virus after chronic therapy. But indeed the pediatric trial is still ongoing and the neurological and developmental milestone data is yet to be collected on that.

In some of our programs we do have quality of life measures. I think one issue to bring up here is the issue about the validation of quality of life measures and whether that indeed as a stand alone would be appropriate as a clinical endpoint trial. But we are open to suggestions of the committee. If there are ideas or proposals that we can examine along the lines of a more traditional clinical endpoint type trial, we will obviously take those under consideration.

DR. MASUR: Dr. Jolson, did you have a comment?

DR. JOLSON: Yes. Again, this gets back to just procedural issues, and I thought just for the sake of having done it, it might be worth reviewing very briefly the difference between accelerated and traditional approval and exactly what the agency means by accelerated approval.

It used to be when, shortly after the regulation was enacted in 1992, that we would routinely do this every time we presented an application for accelerated approval, and after a while it got kind of old and the committee got kind of tired of hearing about it. But since there are many new faces around the table, I'd like to just at least

clarify exactly what we mean by accelerated approval and how it's implemented.

The slide that you showed, shows where it's from in the CFR. It's called subpart H because it's subpart H of the NDA regulations, and it applies exclusively to treatments for serious and life-threatening illnesses that presumably provide meaningful therapeutic benefit over existing treatments, and the regulations cite examples, such as those unresponsive to or intolerant of available therapy, or improved patient response over available therapy. Those are just examples, and there certainly is flexibility in terms of how we define "meaningful therapeutic benefit."

And again, it's based on a surrogate endpoint that we believe is reasonably likely to predict clinical benefit. Here, where the committee has discussed in July of '97 that clinical benefit can be indicated by long-term viral suppression and by that we as an arbitrary point have chosen 48 weeks, so in these studies if you believe that a surrogate marker response has been demonstrated through 24 weeks, we would say, "Well, that's reasonably likely to be indicative of a longer-term response and a longer-term clinical benefit."

The regulations go on to further describe the implementation of this type of approval, and it differs from traditional approval in two important respects. One is that

advertising is supervised in a different way than other advertising.

And also, it's the only regulation, the only type of approval that has mandatory Phase IV commitments. All other Phase IV commitments from regular approvals are voluntary. These are mandatory, and these are the traditional approval studies that we've spoken of, for if they were not to have been done or if they failed to indicate clinical benefit, products would be withdrawn from the market, and those are some things spelled out in the regulations.

So that is why the studies that we have--that we will ask you about, the traditional approval studies, are different in how they can be enforced by the agency than other Phase IV studies that might address other issues.

Let me just ask if there are any questions or any other points of clarification.

DR. MASUR: Well, let's start. Again, for each of those categories, accelerated and traditional, one needs two independent studies, correct?

DR. JOLSON: They can be the same studies. For example, there's nothing to say that sponsors couldn't initiate 48-week studies, submit an analysis between 16 and 24 weeks in support of accelerated approval, and continue them on. So it can be the same two studies.

I think in this case the concern that was raised by the review team was that of the three studies, there was really only one study that was reasonably likely to provide confirmation, and that the package may be somewhat lacking. And so that was a point for you all to discuss.

DR. MASUR: Right. Let's move on. Let me, just to indicate what's going to happen after this, we will read the questions, we'll go over the voting members, and then if the voting members, maybe we could pass around something, Rhonda, so I know what time all the voting members are going, so we make sure that anybody who has to leave early has a chance to give his or her comments.

So start with Jeff.

MR. BLOOM: Dr. Jolson, this is a procedural question. I believe in the past, and I can think of at least two examples where accelerated approval has been granted pending acceptance of a second acceptable protocol or a final end of a protocol, with the FDA and the sponsor agreeing to another trial that would be agreeable to meet the definition for traditional approval. But the accelerated approval was conditional upon that protocol being followed and accepted, or other conditions have been put in place where not accelerated approval which was voted but certainly things had to happen first for the accelerated approval to be given.

Because one of the things that's troubling, I think, and in talking to some of the people sitting next to me, the one trial that you're citing as the trial that meets that standard has the 24 percent dropouts, and as pointed out, depending on what happened with those 24 percent dropouts really does affect how that data is in those two different arms of that trial. So there are ways--I'm asking you, I guess--there are ways of putting conditions on the approval, there are ways of doing that so that it's a way of moving forward but also placing certain conditions prior to granting accelerated approval.

DR. JOLSON: I think my response would be not just for this application but for any application, there is a lot of work that goes on between an advisory committee discussion and the product's approval. And that's why we try to time the advisory committee at least a month or so before the actual action date, to allow time for that kind of work.

And the sorts of things that would have to be agreed upon would include labeling, all Phase IV commitments, and in particular the adequacy of the traditional approval study plans. So those would be things that would need to be agreed upon for us to take an affirmative action.

MR. BLOOM: I'm sorry. Maybe you aren't

understanding my question clearly.

In the past, advisory committees have recommended accelerated approval pending acceptance of a second protocol that was agreeable by the sponsor and the FDA. It was conditional based upon the agreement on a subsequent protocol. And I think that was--I can think of two examples of that, and I was wondering if that's still the case.

DR. JOLSON: Where it would be--

MR. BLOOM: The committee's recommendation.

DR. MASUR: Well, in other words, Jeff, you're saying that if we said there has to be a second study that's agreeable to the agency, that might be a condition for our providing approval--

MR. BLOOM: Exactly.

DR. MASUR: --depending that--

MR. BLOOM: Exactly.

DR. MASUR: That would be one option for us to recommend?

DR. JOLSON: Yes. Yes. Oh, absolutely.

DR. MASUR: Without specifying exactly what the trial was?

DR. JOLSON: Right, right. If you had suggestions, for example, that you'd like to see another study designed to provide comparative efficacy data, 48 weeks, that could additionally address unanswered questions

X, Y and Z, we would then work with the sponsor to at least, you know, get some agreement on the conduct of that sort of study.

DR. MASUR: Jim?

DR. BERTINO: Just to clarify, in my mind Dr. Lipsky's question before for the medical reviewer and the statistical reviewer, are you saying that based on 3005, the sixth slide from the end is where you say short-term surrogate marker changes support antiviral efficacy, but then we heard the statistical reviewer say there was 24 percent dropout, and we're not sure after you take that into account what the--

DR. CVETKOVICH: No, I think the--

DR. BERTINO: I'm not trying to pit you folks against each other, but--

DR. CVETKOVICH: No, no, no. I think that's--I mean, that's a very fair question. I think that I guess what we hesitate to do is really overstate our evaluation of the preliminary results from 3005. However, we have to balance that with the fact that when we requested that data, we knew that what we would have would be preliminary, and we felt that this was required to support or to help flesh out questions we had based on the review of the first two studies.

So it is kind of a delicate balance that I think

you're seeing kind of go on before you. I guess I feel that we did need to make a cut and a decision about what our thoughts on this were, but that we are here today in order to hear whether that can be supported or not. So, you know,--

DR. BERTINO: So then are you saying that of the studies presented today that you reviewed with us, only 3005 supports antiviral efficacy by surrogate marker?

DR. CVETKOVICH: No, I think 3003 did also.

DR. BERTINO: 3003 did that, too?

DR. CVETKOVICH: Yes.

DR. MASUR: And clearly what our role is, as I'm sure you well recognize, is we have to balance what the FDA has said, what the sponsor has said, and our own perspective of the role of importance of various issues, as to whether--which side of the line we vote on, and we'll find out where you stand in a few minutes.

DR. BERTINO: Could I ask one more question about the hypersensitivity, and this is both for the FDA and for people at this table that treat HIV patients. Are there any other antiretrovirals that you see a significant rate of hypersensitivity reaction as discussed here today, other than a couple of reported cases somebody mentioned for indinavir?

DR. CVETKOVICH: I'm unaware of any others,

although I haven't probably gone through every single antiretroviral, but it's not my impression that this is a common adverse event. I mean, this is--rash and that other direction, we have dealt with--but this again I think is a different--

DR. BERTINO: Life-threatening.

DR. MASUR: Well, we can talk about there are life-threatening complications for a number of the drugs. For instance, Stevens-Johnson syndrome, we could probably point to a number of drugs, and I guess what we have to assess is where this frequently of this life-threatening complication fits into the spectrum, as one of the questions that really goes into what the risk/benefit is.

Joe?

DR. HOGAN: I'm still trying to clear up the surrogate marker issue, because in the slide that was just up here it said treatment needs to demonstrate efficacy on a surrogate marker, and yet there seems to be--there seems to be a sense that the new drug should be held to a standard of improving two surrogate markers.

And so I would be wondering, just from the clinicians here, and the statistician, Mike Elashoff, brought up that we're trying to weigh the relative benefits, and I wonder how those are weighed in a clinical sense, because it seems like there is maybe demonstrated efficacy

viral-wise for the adult trial, sort of debatable in the pediatric trial, but maybe CD4 has held the same in both, and so I don't know how we are supposed to evaluate that. If we can maybe make a case or we think in our minds that it does affect one surrogate marker, not the other, is it one surrogate marker we have to hold it to, or two?

DR. MASUR: Well, I would suspect that that's going to come out in the discussion, but I guess we had all hoped several years ago that these would always go together. I guess we're finding out that there are some situations this isn't unique where they don't, and that it is, at least from my own perspective, very difficult to know where to put an agent that affects one and not the other. And fortunately, we're not the Center on Biologics; we don't have to deal with that from another perspective.

DR. YOGEV: But you have to admit that unfortunately we are realizing, when we get to the point that we don't have any other options, that the option of only one marker doesn't change. Because in pediatric we are more now accepting because we have only two options, that if at the end of the second one, either the viral goes up or doesn't come down, if CD4 is changed, we are now collecting data to see if that is really also a good marker for extension of quality that it is at that point in time, to buy time, so-called. So this is a very important question,

which I had an impression in pediatric we are now moving into looking into those naive coming back, and so forth, without viral load being changed.

DR. MASUR: Well, I agree with that. I was trying to be neutral in terms of where I stand on that position.

DR. HOGAN: Just to be more specific and not sound too legalistic, the letter of the law says one surrogate marker and yet we're considering two surrogate markers, so I'm just looking for an interpretation of the mandate for early approval.

DR. MASUR: Yes. Well, I'd be surprised if Dr. Jolson can clarify this, but we ought to give her a chance.

DR. JOLSON: You just want to see how I'm going to answer. That's actually a very good question. Well, that's that flexibility thing, that I think it's--sort of overall, it's the surrogate marker database that we're looking at now. When the law went into effect, there was really only one surrogate marker, so it was kind of easy. CD4 was the clear preference at the time, and everything else, you know, P24 antigen and all those other things, were a little less interpretable.

I don't think you should feel restricted that it's an either/or, and that's really why it's here in front of an advisory committee, because in at least one study there's somewhat conflicting results in terms of the magnitude of

the treatment effect. And that really I think is up for clinical judgment in terms of how those are interpreted and how the different results are integrated together, but you all don't have to worry about the letter of the law in terms of your interpretation of it.

DR. MASUR: Yes, and I presume that, again, one of the reasons it's at this advisory committee is that the agency would like our advice on what to do, and clearly it isn't a very clear-cut issue.

Are there other procedural issues? Because, again, I do want to get to the questions. Linda, do you or Steve have a solution to this. Not that we necessarily--

MR. LA FON: Well, we do appreciate the complexity of this, and obviously we have been working with the agency to try to address some of these issues. I just want to make some points in discussion here.

One, we are in agreement that 3005 is an appropriate traditional approval study, with the agency. We are also in agreement that 3003 will only be supportive. As a matter of fact, we have 48-week 3003 data which may help with the CD4 discussion.

3006 is a little bit more complex, and I think Dr. Yoga was bringing it up. We seem to find that result where the viral load response, significantly different, not significantly different, the response is not near as

profound as we have seen in adult naive patients. However, we did see a CD, a positive CD4 response, and while the FDA's review indicated there was numerically an advantage, as a matter of fact our analysis showed a statistically superior response to CD4 in that group.

I think thirdly, and probably most importantly, as we mentioned earlier, that trial is collecting neuropsychological endpoints and development milestone endpoints which will be available at 48 weeks. So that data may be appropriate for discussion around the traditional approval package.

I want to just briefly, and I appreciate, and we'll talk about the caveats of this, want to show the 48-week CD4 data for 3003.

DR. MASUR: Steve, let me just--for everybody speaking, we need to truncate this, because otherwise some of the voting members are not going to have a chance to make any comments. But ago ahead at 78 speed.

MR. LA FON: Okay. This is the absolute CD4 cell count through 48 weeks of treatment. We have provided this just very recently to the agency, and so will accept that it has not been reviewed and has not been discussed. And this right here is the--let me find it--this is the 16-week point.

The bottom line is that both groups--and again I

mentioned earlier, most patients switched on the double to open label abacavir/3TC/zidovudine, and both groups are showing a similar CD4 increase through 48 weeks. The bottom line is, and unfortunately we don't have this plot, the median increase in CD4 cell counts through 48 weeks of treatment was 152 cells in both treatment groups. So while at 16 weeks we were showing, you know, less than 100 cells or possibly a 100-cell increase, that continues to increase.

DR. MASUR: Are there other procedural issues before we move ahead?

[No response.]

DR. MASUR: All right. Let me then read the questions for the advisory committee, and then we'll start with the individuals who have to leave first. There are seven questions that have been proposed to us:

Number one, are the available data sufficient to support accelerated approval of abacavir for treatment of HIV? If no, what additional studies are recommended? If yes:

Number two, the principal abacavir-containing regimen studied in Phase III trials consisted of three nucleosides. Please comment on the appropriate use of this regimen and the appropriate patient population..

Number three, please provide your assessment of the risk/benefit ratio for abacavir and the implications for

clinical use.

Number four, several marketed antiretroviral agents associates with rash are likely to be used in combination with abacavir. Please provide your recommendations for the management of patients developing rash while receiving abacavir in combination with these agents.

Number five, please provide recommendations for disseminating information on abacavir-associated hypersensitivity to patients and providers, and what further studies of these reactions should be recommended.

Number six, please comment on the applicant's proposed traditional approval package.

And, number seven, please provide recommendations for any additional Phase IV studies.

So those are the seven questions, and again, in the interest of making sure that we get the comments particularly of five individuals who have to leave before 4 o'clock, why don't we start with Dr. Pomerantz?

DR. POMERANTZ: Thank you for allowing me to go first. First, I do think that I would support--I will support the accelerated approval of abacavir for treatment of HIV infection. So I guess since I said yes, I should go on with the other questions, or do you want to take a vote around the table for one and then go back to the comments?

DR. MASUR: All right. Let's see if we can do that expeditiously. Do you want to make any comments, any other comments about number one?

DR. POMERANTZ: No. I say yes, and then I'll go into why I say yes and two through seven.

DR. MASUR: all right. Well, this is actually--I thought we would do through all of them, but I think that's a more reasonable idea. Why don't we--we'll start there and just go around the table on number one. And then again, if we start running out of time, we will get Dr. Pomerantz go through all of them, but let's do number one.

DR. HAMILTON: I would say I'm reluctant to support the approval for traditional--or for accelerated approval.

DR. MASUR: Do you want to make any comments, John, any editorial comments?

DR. HAMILTON: I have some I can make, but--

DR. MASUR: Why don't you make them briefly, and then again we will move on.

DR. HAMILTON: Well, it seems to me it hinges on question number six: Are there the appropriate elements to accept this in the usual framework? The message I've gotten today is that 3005 is the only one that's currently constituted to answer the question. That's one study. The others are either not going to provide that data for sure or

are very marginal. My sense would be that there needs to be some additional work to support that proposal.

DR. MASUR: John, if I understood--again, maybe we ought to ask Dr. Jolson to clarify this--but if the agency could come to an agreement with the sponsor as to two studies that would support traditional approval, even if they're not underway, if the agency were satisfied that there were two traditional studies that could be gotten underway, would you feel the same way? In other words, if there is another study negotiated.

DR. HAMILTON: It would all depend on what the study was that they were proposing. I'd like to see what--you know, what there is. Where's the beef here? And so it just seems like we're pushing back the approval process further and further without a compelling reason to do so. We're proposing to approve this drug so that it can be accessible to patients who need it desperately, and the fact is that there certainly are patients who do need it desperately.

However--I'm not trying to get in the way of their having access to it, now that by the good graces that it has been made available for some number of people on expanded access, and they are to be applauded for that. I don't think, however, that licensing it or recommending that it be licensed provisionally necessarily is going to have a major

impact. I mean, think of where we are thinking of using this drug.

We're thinking of using it in a population of people who already have gone a long ways down the line. They've tried a lot of drugs, and what have we gotten from it? What we've gotten is a whole lot of resistant drugs. Granted, we've also had some major benefits in the form of what seem to be dramatic changes in survival. Those benefits have been attributed to the protease inhibitors. I don't know if that's true. I have some doubts that that is the entire explanation.

But I think to prematurely put another agent out there without a compelling reason, one that I guess lives up to the standards that have previously been set by this committee, I think would be--to me it would be a mistake.

DR. MASUR: All right. Let's go--we are going around getting each person's decision. Then we will do a formal vote, and again, I'll read the list at the end of this as to who the voting members are, but there are 10 voting members today.

Dr. Matthews?

DR. MATTHEWS: I believe adequate evidence of efficacy has presented, particularly with the 3005 preliminary data. I have major concerns about safety, not so much within the trials and expanded accesses that have

been described, but potentially in a much looser context once the drug is available by prescription. On balance, I'm going to vote "yes" with assurances that an adequate safety package is put together subsequently.

DR. MASUR: Dr. Wong?

DR. WONG: I guess I would just like to make a comment and maybe a question to the FDA reviewers. When I read the results of the pediatric trial, I really came to a different conclusion: that these data do show efficacy, or at least that if this study is carried out until the end, that there is a reasonable chance that they will demonstrate efficacy that is durable.

And I understand, you know, that the less than 400 endpoint was not the one that was originally included in the protocol, but that doesn't mean that it's not relevant information. And I think I would like to hear why it is that your bottom line conclusion is that this study is unlikely to be supportive of efficacy for this drug, in light of these graphs, especially with the less than 400 endpoint showing to me a clear superiority of the triple combination as compared to the double.

DR. CVETKOVICH: We have--perhaps we haven't made our position as clear as it might be. I believe that we're not quite sure what do with this protocol-specified endpoint of 10,000. Clearly when the study was designed, time has

passed, we know more now. Hopefully we're moving toward more and more effective treatments for kids.

So we're kind of looking at two endpoints and somehow trying to say what this means in terms of efficacy. I think that clearly there are patients who have benefited from this treatment in the pediatric study. I suspect that those are the ones who have received the shortest previous treatment and the least exposure to zidovudine/3TC.

And so I think that we do have pieces from this study which are supportive of efficacy, but on the whole, given that we only have 12 percent at 16 and 24 weeks in the abacavir-containing arm versus 2 percent in the ZVD/3TC arm, and the study isn't even halfway through, it's very hard--or it is halfway through and has halfway to go--it's very hard for me to see that with another six months that's going to give us a whole lot more.

DR. WONG: I guess my reaction to this is that, you know, I'm afraid that we might have put ourselves in the position of being almost prisoners of the criteria, and since we're going to--you know, since we will have numerical data that's continuously variable on efficacy, why not analyze it that way, rather than say, you know, count up the yeses and noes at 10,000 and count up the yeses and noes at 400.

Why not just ask the question at the end of the

study, or at interim points through the study, you know, what is the net reduction in viral load per individual over time, comparing the two groups? It would seem to me that although we can't predict the outcome at 48 weeks, I think it's too strong to conclude from the data we've heard today that this study is not going to support efficacy. I think it's an open question. And for that reason I would say that the sponsor has shown what they need to show today, and I would vote for accelerated approval.

DR. MASUR: Okay, and we'll come back to that before 3:40. Let's see if we can get around relatively quickly.

Skip?

MR. O: I'm probably the newest member here. Well, I'm not a member, I'm a consultant. But I'm not really compelled by the data that have been presented here today, and I think if I had to vote right now, I probably would vote against it.

Very quickly, I am bothered by the so-called anomalous result in the adult study, the 3003, and I am also a little bit bothered by the very high fraction of people who were enrolled in the study, the pediatric population, who actually were less than 10,000. Twenty percent of the individuals actually had the endpoint at baseline. And I am troubled by the 24 percent dropout rate in one of the

studies that's going to be used to actually support the traditional package.

DR. MASUR: Okay. All right, and again, we'll come back to some of these issues.

Joe?

DR. HOGAN: I'm not actually a voting member today.

DR. MASUR: But I'd like everybody's position, and then again we'll get back to the voting members, to vote.

DR. HOGAN: Well, my position would be not quite binary, more of a conditional yes, and I know that that probably reveals my being a rookie here, to give an answer like that. But here are some of the concerns that I have.

DR. MASUR: Actually, Joe, if you don't mind, if I could come back, if we can come back to you, because if it's going to be conditional, that will have to do with some of the things in two through seven, I think.

DR. HOGAN: Yes.

DR. MASUR: So if I could, we'll come back to that.

DR. HOGAN: Yes. Okay. So I would say it would be a yes, but under some strong conditions.

DR. MASUR: Okay. Joe?

DR. BERTINO: Something on Dr. Jolson's memo that she sent to us, under "Issues": "For accelerated

approval...effect on surrogate endpoints sufficient to conclude that the drug may provide meaningful therapeutic benefit over existing therapies." Using that definition, I would vote "no" unless Dr. Jolson wants to tell me different, that I am interpreting that wrong.

DR. JOLSON: Well, I think that there is a couple ways that you could look at this product as at least being consistent with that criteria. In terms of providing meaningful therapeutic benefit, it's in someone or in some population, so whether it's in patients who have limited options, that this might provide benefit through demonstration of an antiviral effect, or by virtue of being used in a triple combination it would provide another treatment option. So those are at least two possible ways that you could say that it is providing benefit, and the sponsor may be able to add to that in terms of what the argument would be for how their product fills those criteria.

DR. MASUR: Okay.

DR. BERTINO: Then I'll vote "yes."

DR. MASUR: Okay, and we'll come back to this.

Jeff?

MR. BLOOM: I think it's rather unfortunate the way they actually have done these studies. I think it doesn't meet the threshold for accelerated approval simply

because we do have a lot of therapies on the market now. We have a lot of people that are pretreated with AZT and 3TC, that may use this with other nucs in a triple-nuc regimen, but we really have no idea how it would work in that regard, and it's unfortunate they really didn't study it with a wider variety of antivirals, nor are their follow-up plans currently to study it with a wider variety of antivirals.

And when asked this question before, the answer was basically, "Well, it's convenient four-pro regimen." There is a current five-pro regimen that is available with combavir and sustiva that's pretty convenient and available as of now. So given that, and given the fact that there really is only one study with that 24 percent dropout, I would think that gives me pause to concern. Because if throwing another--people do need more treatments and people need more therapies, but we need effective therapies, not to just throw them out there.

DR. MASUR: Okay. We'll come back to some of these issues that need to be followed up.

Frank?

DR. GIGLIOTTI: I guess one of the key things is whether the pediatric trial suggests efficacy or not, and again, I would agree with Dr. Wong's assessment, that as I look at this, that I think while a 20 percent rate of having less than 400, a viral load of less than 400, isn't

terrific, in the population studied I think it is significant, and the control group is approaching zero. So if you look at it the other way, 10 times as many people have success virologically. That's a small number, but I think that does indicate efficacy.

And as I look at these numbers, it looks--there was concern this morning that there are not going to be enough because that offer of a switch-over at 16 weeks, although blinded, was going to interfere with the analysis. As I'm looking at the numbers on the slide, it looks like there's at least 90 people in each group that have passed the 16-week point, and so you have that--and I don't know if that's because the rest of them have switched or that the others have not reached that marker, but it looks like there's going to be a least 180 kids who will be followed for the full 48 weeks, and I think that will give you some data. So I would be inclined to favor it, although I am not fully--

DR. MASUR: Okay. Well, again, we will come back.

Ram?

DR. YOGEV: I'm a little bit different on pediatric. I think we are seeing--people compared to others, because there were too many patients on those AZT and 3TC, and that's basically on--300 or 150 to ACTG. So I don't think on science I approve it.

On the other hand, I think compliance is a major issue which we somehow avoided. In pediatric it is a major problem to supply a combination that will give us the same efficacy, at least for a short period of time, until we get the trust of the patient, until the patient is getting used to taking those drugs or taking few, getting the same efficacy, make a point that you might consider.

So on science, no; for patient convenience, maybe have compliance, yes.

DR. MASUR: Okay. Pam?

DR. DIAZ: There are some very concerning issues, but I feel that I probably would approve it based on efficacy and safety, but again, somewhat conditional in the sense that in particular the 3005 study, which is the one study that we're all sort of hinging on getting data in the long run on, our 16 and 24 week data is not really finalized, and I think that would in my mind have to be more succinctly put together in order to give accelerated approval.

I too am not as skeptical about the pediatric study not showing anything in the long run. I think that it might provide some additional data, but I certainly wouldn't hinge everything on that. I would expect a second study to be instituted and conceived for traditional approval, and again, I think it would depend on what that study was as to

whether approval should be given unconditionally at this point in terms of accelerated approval.

In terms of the safety, again, I think it would in my mind depend upon the package that's designed for the education and demonstration of this drug in terms of its safety. And again, I think the Phase IV commitments would be--I would need to see those in my mind, but I do believe that there are a group of patients out there that would benefit from this drug, and because of that I would vote "yes."

DR. MASUR: Okay. I'll come back to my comments in a moment. Wafaa?

DR. EL-SADR: I'm glad I'm not voting today. This is very difficult.

I guess it's just a little bit concerning that we are hinging everything on the equivalent study, 3005, where the--we didn't have really a chance to look in detail at the study, and the agency didn't have a chance to review it in detail, but I think that's the one study that's reassuring.

I'm very concerned about 3003, with the discrepancy between the HIV RNA and the CD4 cell count, and also about the pediatric study, because I'm not sure that this study will demonstrate any superiority of abacavir in the arm where it's being used.

I also am concerned that we haven't really seen

good data on any efficacy in the experienced adults. So a lot of ifs, and--

DR. MASUR: All right. We will come back to your "ifs," and there are going to be a number of "ifs" to come back to.

Jim?

DR. LIPSKY: Okay. I won't "if." I would say approve it for accelerated approval. By the nature of that approval process, that is a conditional approval, and once this committee by your predecessor pointed out that there have been so few times when drugs haven't gone on to, you know, the traditional approval, that maybe we are a bit too stringent. We are, you know, too stringent, or even having the drugs brought forward.

So anyway, yes, I think there is antiviral efficacy there, enough for--on one surrogate marker, which is enough for accelerated approval. There is the worrisome aspect of the toxicity. In general, toxicities are often worse in situations where they are out of controlled clinical trials. I mean, I think that's aware of everybody--to everybody, including the manufacturer.

DR. MASUR: And my position is to favor approval with a number of caveats. I guess, as with everybody else, I'm troubled by the apparent discrepancy between immunologic and virologic response, and would like to be assured that we

will have the safety program and the traditional approval studies in place before accelerated approval were given.

But I agree with Jim that we need to--I think that this is an appropriate indication where we don't have all the data we would like, but I think we have enough data to put this out. And I would hope that the agency has the courage of its convictions, that if it approves a drug for accelerated approval and either efficacy is not ultimately shown or there is more of a safety problem than was initially recognized, that they would withdraw their approval, and I guess that has not happened yet but potentially could happen.

So, again, so that we can get some of the comments from other people in a moment, the voting members today are Drs. Diaz, Hamilton, Masur, Lipsky, Pomerantz, Hamilton, and consultants--oh, I'm sorry--and Drs. Bertino, Matthews, Wong, and Woolson. So if those individuals could answer the first question: Are the available data sufficient to support the accelerated approval for abacavir? We will take a yes/no vote, and then we will come back to issues two through seven.

So of those nine individuals, how many vote in favor of question number one?

[A show of hands.]

DR. MASUR: And how many vote opposed?

[A show of hands.]

DR. MASUR: So fortunately the math comes out. It's seven in favor, two opposed.

With that initial--or with that vote, with that final vote, the issue is now about addressing questions two to seven, and we'll do that in order of which people have travel commitments. And again, we do appreciate the committee members and the consultants for taking a day out of their lives to come to this meeting.

Dr. Pomerantz?

DR. POMERANTZ: Yes. Thanks again. As you heard, I voted "yes" with some of the problems that each of us have faced. I mean, it's clear that this wouldn't come to committee unless there was a difficult series of choices.

And that being said, going to number two, where it's asked, "Please comment on the appropriate use of the three nucleoside analog regimens," well, this is not just for abacavir but it seems to be a general question in the field, and it's one that remains somewhat unanswered. Abacavir is interesting not only because of its resistance profiles but also because of the strength of its monotherapeutic effect.

This--if one of the three nucleoside analog regimens is really going to hit the full tilt of comparing to a protease inhibitor regimen, it may be this one, but I

fully agree it's not been shown conclusively. I actually thought that the company would be showing more data today than they actually did, even though they hit the level that I found necessary to make accelerated approval.

Three nucleosides, as I said, have been over the last year somewhat anecdotally stated to be not as intense or to have the duration of effect of a protease inhibitor containing regimen. I think that a number of studies are going to have to be done here, and I'm not fully convinced that in the long term, as you heard from my earlier questions about is this less than 50, how long have you carried this out to, whether it will be truly equivalent or not.

So I wouldn't say up front that in patients of mine, that I might use this as protease sparing initial effect, but that's not what we're being asked today. I think for certain patients who can take protease inhibitors, or those that have not had good results with them, both with side effects and others, that this is a perfectly reasonable second regimen. I'd like to see it become a first regimen, but I certainly don't think that's there yet.

Number three, where it asks for the risk/benefit ratio for abacavir and its implications for clinical use, that's sort of an open-ended question that you've heard a lot today. This is really the first drug, as you all know,

that has a hypersensitivity effect that is more commonly involved with having such serious effects, rather than typical rashes we're used to with some of the drugs that we give both to inhibit HIV and otherwise.

I think that the risk/benefit, there is a higher risk/benefit ratio here than in most of the drugs that we give out to patients who are HIV-infected, but I don't think it reaches the level where it should not be part of the armamentarium of the United States at this point. But, as we'll get to in a minute, this is not a trivial issue, as a variety of people, including Dr. Hamilton, had mentioned.

I think, though, that this can be taken care of by very critical attention by the company, not only by announcing it at meetings but also doing what you're doing now, which is to go out to the grassroots. As was brought out before, it's not just the experts in infectious disease or in HIV therapeutics that need to know about this, it's the people in the walk-in clinics, it's the people in the emergency rooms who will come--who will see these patients on weekends when they get their flu-like illness, and this is something that should be generalizable, as I think and hope that you will continue to do.

Number four, several marketed antiretroviral agents are associated with rash, although if you look in the PDR, I would say that you couldn't find a drug that doesn't

have rash somewhere in that list. So we go through very commonly in patients, either HIV-infected or otherwise, who have rash, to prune away the usual candidates.

This is a different story, obviously. This isn't a rash that will slowly go on to Stevens-Johnson at the worst, or erythema chronicum major at the best, but this is something that could kill you. And obviously, therefore, as we have talked about before, I think that this is absolutely necessary to bring out into the community outside of the HIV experts.

And I think that as well, one group that I forgot to mention is the pharmacists, not just those in the tertiary care centers but the pharmacists in the small pharmacies throughout the country that need to learn about this. I've been very impressed with how they have kept physicians such as myself out of trouble in the multipharmacopeia of patients. So I would again stress that the company try to work on pharmacists, not only in the tertiary care institutions.

And I think I've dealt with number five as I talked about number four. You know, again, I think that it's important that the traditional approval not be thrown aside, as has been brought up by a number of people, including Dr. Hamilton. But if something could be developed between the company and the FDA to make absolutely sure that

happens. Clearly we don't want abacavir to be the first of the drugs to get accelerated approval and then get into trouble because no studies were designed to look well for traditional approval, although I doubt that Glaxo Wellcome will do that, but I think that the FDA will keep good look on that and make sure that it gets accomplished appropriately.

Phase IV trials for abacavir, clearly one of the things that was brought up at the other end of the table is that it would have been nice to have seen more data on other combinations with drugs that are out there besides combavir. Knowing that there are protocols out there, both in the United States and in Europe, I was not overly taken back to the fact that I couldn't approve the drug on that count, as was discussed, although again, I would have thought that some of those trials would have been near completion, which I guess they are not.

There are a number of drugs, both on a molecular biological level that I had mentioned earlier, that may have theoretical reasons why they may do better than combavir with abacavir, but I think that most of the people at Glaxo that I've heard present here and around the country have those drugs in mind, and I would imagine that there will be other studies that will change the way we even look at this drug within the next six months.

And those are the feelings that I had in moving forward with an accelerated approval.

DR. MASUR: Okay. Well, I appreciate, we appreciate those comments.

Dr. Matthews, your plane is next.

DR. MATTHEWS: I'll make some accelerated comments.

On question two, I don't think the long-term comparability of a triple nucleoside regimen has been established vis-a-vis the PI or NNRTI-containing regimens, and so I wouldn't use it up front. On the other hand, there are some definite populations where I would view this kind of a regimen very favorably, and those are the populations who have various contraindications to drugs that affect the P450 system, so that would include people who are on anticonvulsants for either psychiatric disorders or seizure disorders, and despite the fact that the latest MMWR has anointed rifrobutin as the candidate for tuberculosis treatment regimens, I think a regimen like this may have a role in people who are either being ruled out or have tuberculosis.

One other comment I wanted to make. A number of people have commented on the pediatric trial being brought forward as part of the package, and I want to not only echo that but also the notion that trials can be brought forward

as part of the approval package in salvage regimens, which, you know, if you think about it is quite a daring thing to do. And having been at ICAC recently and listened to a whole session on salvage, it's pretty dismal, the results that have accumulated.

I think while the venue here is different, we clearly can't approve a drug based on good intentions in treating populations which have a low probability of response no matter what you give them, still I think it's important that these kinds of trials be continued. That's more or less as an aside.

With regard to question three, the risk/benefit ratio, the risk is the issue in my own mind, and I think that there need to be additional analyses done to identify predictors of the hypersensitivity reaction, and these analysis need to be in particularly--using particularly challenging subsets of data. It's not just enough to say a person is, say, on two other nucleosides and has abacavir and then has a particular syndrome within six weeks of starting, because the fact is that most of these patients, at least in expanded access, are started on multiple drugs simultaneously, and it is not an easy problem to distinguish efavirinz reactions from this reaction.

I have been to meetings where doctors get up and give testimonials on how they can distinguish these things,

but I don't think we've heard any data about how accurate physicians are, particularly when there are cases that cannot be resolved very easily in terms of what is a reaction and what isn't a reaction and this large group of nebulous, maybe kinds of people. So I think, you know, the definitive cases and the people, as Dr. Wong pointed out, who were considered as potential reactions but didn't have reactions on re-challenge is an opportunity to apply some statistical modeling to identify these predictors.

I was pleased to hear about the physician hot line, although I think that once the drug is made available for prescription, that that really needs to be promoted and publicized both for providing information for physicians on how to manage a patient and how to recognize--as well as how to recognize it, and to continue to accumulate data, at least until the time of traditional approval, on the full spectrum of this syndrome. Because, you know, I'm not convinced at all, and Dr. Hetherington acknowledged this, that we understand the full spectrum from the least severe to the most severe, as well as the perhaps uncommon reactions that may not have been present yet.

Let's see. With regard to rash management, there are several subsets of syndromes that I think clinically have to be dealt with. One is the person who has rash alone, and in that sort of situation I think it's reasonable

and many people would just continue treatment, follow the patient closely, and see what happens.

The constellation of rash and fever in my own mind would lead probably, if the patient is on abacavir with or without other drugs that could produce rash and fever, that one would tend to stop all drugs.

The more problematic groupings of symptoms would be rash and just fatigue and malaise, or rash and nausea and vomiting. What does that mean? Because those, the latter symptoms are so common and could be due to almost anything. So one would have to use "clinical judgment" in that context, but what is clinical judgment, and is clinical judgment, and is my clinical judgment the same as yours?

You know, I think one of the things the company needs to do is to study groups of physicians presented various scenarios and see how much uniformity of opinion there is on what people would do in managing these kinds of patients.

With regard to question six, the approval package, I agree that another trial needs to be mounted. The question in my own mind is that, you know, ideally the greatest shot for showing efficacy would be in a naive population. If it's going to be in an experienced population, then I think there should be a prospective stratification on genotypic resistance so that we could get

some useful information on what subsets of patients with various mutation patterns are likely to respond. And there was a very instructive article in JID in September that Scott Hammer co-authored, that illustrated how resistance testings could be included in a factorial design to study agents like this.

And I don't have any additional comments on question seven right now.

DR. MASUR: Dr. Jolson, I missed the fact that you had a comment you wanted to make. Do you have any comment you want to make now?

DR. JOLSON: Well, it's again just back to the traditional approval package in terms of the studies, and I don't think that we're saying that it would be impossible for the pediatric study to demonstrate a treatment difference at 48 weeks. I think that our concern was that it's somewhat risky, given what the analysis at 16 and 24 weeks looks like, that at least with the less than 10,000 cutoff, that the arms are approaching each other, and that if you look at the less than 400 cutoff, the rate, the overall rate in both arms is very, very low.

So from looking at it from that standpoint, even if we believe that there is evidence of some limited, you know, evidence of efficacy during that period of time, it becomes somewhat risky for the sponsor to assume that we're

going to see a robust treatment effect at 48 weeks. It seems somewhat unlikely.

And that's not at all to diminish the importance of a pediatric study or 48 weeks of pediatric data. We definitely want to see that data. We want to see the study completed and submitted and incorporated into any labeling, but it just is somewhat risky to bank on that as one of two pivotal studies, because it can't be assumed that the equivalent study either is going to pan out.

So again, it's risk, and it's not in any way to say that it's not an important study or doesn't contribute to our understanding. So I just sort of wanted to put that into the context of thinking.

DR. MASUR: What procedurally would occur if six months or a year from now, one study supported efficacy at 48 weeks and the other did not? At what point would you feel obliged to pull the plug on the accelerated approval?

DR. JOLSON: Well, this would be the--whatever application, accelerated approval application comes in with the first traditional approval package based on 48 weeks of viral load data, that will be the first. And I would think--and, you know, we also might entertain bringing it to the committee.

I don't know that--I don't know what the sponsor's plans are in terms of the timing of the studies, if both

studies would come in at the same time or if they would be staggered, because sometimes we'll see traditional approval applications that are staggered, that will only include--

DR. MASUR: Right, but I guess what I was suggesting is if one is--if the pediatric study in fact turns out to show no difference--

DR. JOLSON: Uh-huh.

DR. MASUR: --for the reasons you indicated, the other study does show a difference, then you're faced with the fact that you have to start another study that will take a year, two years, three years.

DR. JOLSON: Well, I think we would probably be back here in a setting like this at a Holiday Inn, you know, somewhere in Montgomery County, and we would sort of probably be asking the committee, given the totality of the evidence, do we believe that clinical benefit has been demonstrated?

My preference would be not to assume that studies are all positive or all negative, even if they don't--because even if they don't reach a certain p-value, sometimes we can get important information, and I think in the pediatric study some of the maybe differences between a biometrics review and the clinical review is based on the fact that even if a particular endpoint wasn't reached in a robust way, we can still conclude that there is some

evidence of efficacy there.

DR. MASUR: Okay. Quick comments, Ram?

DR. YOGEV: I just wanted--I am a little bit confused, and maybe you can clarify to me. Nobody in your--until just recently there was a recommendation how to treat a pediatric patient, and do a therapy on a patient who is experienced with any one is not indicated, and are we saying that in taking a study which is basically close to placebo, monotherapy, to compare this treatment, and if it show even efficacy, we accept that?

My problem is that the study design at this point in time is not appropriate, and one would like to see something else, not even to wait for those results, because if you show efficacy, it's what happened to us in 152. We said that ddI is as good as ddI/AZT because we didn't realize we are dealing with a placebo.

DR. MASUR: Dr. Jolson, we'll ask for a quick response, because one thing, I'd like to make sure that with Dr. Wong, Dr. Lipsky, and Dr. Hamilton if he's coming back, that we get their comments in before 3:40.

DR. JOLSON: Yes. I guess I think your point is well taken, and just in a one-sentence response, I think that is what we would hope to hear when we ask you to evaluate the adequacy of the traditional approval package, would be to take those issues into account in terms of the

types of questions that studies can answer and how clinically relevant that information will be.

DR. MASUR: Okay. Well, for those of us who are staying a little later, we'll come back to that, but Jim?

DR. LIPSKY: Okay. Thank you. First, I would also like to congratulate the sponsor on the pediatric studies and complement them for bringing them forward at this time. This committee in the past, as some remember, heard an impassioned plea from the public to not ignore the pediatric population. I'm glad to see that that plea has been listened to.

On the use of three nucleoside analogs, well, it would seem that theoretically a more rational approach would be try to hit the virus at two different targets. Of course there is the issue of mutation resistance which at least dual nucleoside therapy has demonstrated. But what one would--one would think that this probably wouldn't be the answer of a long-term therapy, but again, that is theoretical. And I think that several people have already talked about, you know, appropriate use, and it probably wouldn't be an initial therapy although it might be part of it, or it might be useful to some people to have a twice-a-day regimen.

The risk/benefit ratio in part may have something to do with question two, in other words, who are you going

to use it in? If there are other drugs available which have, in combination, good antiviral response, and you have another combination but one of the drugs may be associated with fatality, which is different than the others, then that may--that may change the risk/benefit ratio. I think, though, it's a little bit confusing with multidrug regimens exactly--exactly what's going on, so it may be--I think it's a bit premature to see where that will--where that will come out.

The recommendation of managing patients with rash, it looks like this drug may be the first one that you'd want to discontinue if you had a variety of agents and developed what looked like a hypersensitivity problem.

We talked about recommendations and the proposal for a traditional approval package. Well, I don't think the sponsor is naive and I believe that they would be looking very carefully to see what is going to make the best package and would work with the FDA. It's hard to, you know, come up, here's the study, here's the study to do, but I'm sure the company doesn't want to see this--you know, the efforts of this drug go to waste, and I think that will be an important, probably an important task which they are probably undertaking at this very moment, and I'll end there.

DR. MASUR: John?

DR. HAMILTON: It's great following Dr. Pomerantz and Lipsky and Matthews, and I don't have to say that much, but in this case since I voted differently, perhaps I could say just a few words, supplement what I said earlier.

I think underlying my position here today is that I don't consider the undetectable plasma viral load as being the Holy Grail of treatment of HIV, a view that I'm happy to see some pretty prominent AIDS investigators are supporting as well, including Jay Levy in The Lancet a few months ago, including David Cooper very recently, and others. I think there's a larger picture here. Efficacy is one thing. Effectiveness, effectiveness is another.

So I guess perhaps then I intentionally, and certainly unintentionally as well, hold the sponsors to something of a higher standard than perhaps they have been given marching orders for, and I know that's possibly not fair also. They have been given a task and, as you saw, seven of nine agreed that they had done so. And I don't altogether disagree with those votes, though I would continue to say I think there are some supplementary pieces of information that I think we would all profit from, and hopefully those will be provided in the follow-up period, in the course of pursuing the traditional approval.

Those comments having been said, I think my interpretation of the risk-benefit ratio here would probably

be self-evident. It depends on what you mean by "benefit." We are instantly attaching some risk here in the form of a new drug with a potentially serious side effect, perhaps not.

But I'm always concerned when something serious happens in a smaller number of patients and you then put it out in that larger number of patients, with health care providers who perhaps are not as well informed, who may inadvertently re-challenge these patients and have a much larger problem than we see in clinical trials. I think that wouldn't be all that unexpected.

In addition, efficacy traditionally falls when one puts a product in the general population, so this drug too is not a miracle. On the other hand, it may well provide some benefit. We heard, as I said earlier, some impassioned testimony from one of my duramites today, and he means it. And I'll say that I have known this man for some time, and he looks a lot better, there's no doubt about it, and I'm glad for that.

But I think efficacy or cost/benefit here is highly dependent on the definitions that one imposes. If one requires actual quality of life benefits and, you know, feeling better from day to day, well, there are ways to measure that. Symptoms are included. Simple pill-taking can be an adverse side effect of sorts. In this case they

may have simplified that. That's good. It's not reason enough, however, in my view to provisionally license this drug. Nonetheless, it's good.

So risk/benefit, yes. I don't know. I don't think we're going to have a fair measure of that. I would be reluctant to use three nucleoside analogs, personally. It just doesn't make much sense to me. Have I done it? Probably. Will I do it again? Probably. Would I recommend it? No. The problem is, we're running out of drugs here. To that extent, I am extremely grateful for Glaxo Wellcome's commitment to this area of research and drug development.

The rash, potentially serious. I already mentioned that I think it's going to potentially get worse once this gets out into the community. That remains to be seen. I think to take all the appropriate advisory, educational efforts that have been outlined, and others, is completely appropriate and I hope will be done.

Inevitably, however, people don't always get the message. I mean, those of you who have been in the AIDS field for any period of time whatsoever realize very quickly that even the message of transmissibility and infectivity never seems to reach receptive ears somehow. It's always astounding to me that that's the case, and I can imagine that this message too will fail to reach a lot of people. Hopefully they'll keep track of it, though, "they" being

Glaxo Wellcome, and if there's anything serious, why, something will be done, and I have confidence that that will happen.

And I've addressed briefly the dissemination of information. I'm not certain I have any idea what to recommend for Phase IV studies. I'd like to see us get through Phase III, and then--and then think about it.

DR. MASUR: Well, that's the virtue of being an advisor, not a member of the agency.

Dr. Wong?

DR. WONG: I guess I voted for accelerated approval. I agree with virtually everybody else that I would have liked to have seen a more complete set of data to justify that, though, but I guess on balance I came down on yes.

You know, with respect to these specific questions, you know, triple nucleoside analogs, I guess it should be an option, since we don't have that many options. And then I considered questions three through five really all to be the same, in the sense that we don't have enough information to draw any conclusions on these points, and I would put it right back to the sponsor, that I think it should be up to Glaxo Wellcome to generate clear data on the benefits and risks, and particularly about how to handle possible adverse effects.

I don't think we really saw enough information to draw any firm conclusions about what really is this syndrome. For example, there were no controls, and I think that we need some--you know, some careful and rigorous clinical research here to describe this syndrome and also to work out what the best way to handle this syndrome should be, even if it takes prospective studies to address that point.

I don't think I have anything to add on the traditional approval package. I hope the pediatric study works out to be definitive, but if I were in the sponsor's shoes, I would not count on that and would mount another study. And I think I agree with Dr. Hamilton on Phase IV. We need to finish Phase III.

DR. MASUR: Okay. Skip?

MR. O: Sure. I'm one of the two that came down on the other side of the coin, although it was a very difficult call for me. I would--as we move forward here, I think it would be very helpful if we could see some plans in the future or something worked out with the agency with regard to formal analyses of the risk/benefit, and particularly the safety analyses. We talked a little bit about that today, but I think that there are a lot of analyses that can be undertaken to take a look at factors that might predict hypersensitivity, and I think it would be

very useful for those things to be undertaken and for those things to be part of the traditional package that comes forward.

The issue of the 24 percent dropout, not to keep mentioning that, but since this is one of the pivotal studies now for the traditional package, I think it really would be important for the agency and the sponsor to get together on that matter, and I'm sure that they have, for the reasons mentioned here, but I am concerned. The point made by Dr. Elashoff that the 24 percent dropout in an equivalent study tends to make the groups more comparable, so in a sense that's a little more problematic than it is with an efficacy study, and I think that that issue will need some careful attention.

I still do believe that the data that were presented here today largely support a benefit, if anywhere, in the group that is treatment-naive. In particular in the adult and then even among the pediatric population, it's those individuals who had no prior--I realize it was both therapies. That's where the effect seemed to be seen. And so the experienced population is one where the likelihood of benefit really is going to be small.

I'm not sure I have anything. I think that's about all I have here, Henry.

DR. MASUR: Okay. Thank you. I guess the next,

going in an order known only to me, Wafaa?

DR. EL-SADR: I'll go to question number two. I think the question of three nucleoside analog therapy is a question that's an unknown, and probably the ongoing study will demonstrate whether this is a viable strategy, since this is the study that's comparing triple nucleoside versus a PI-containing regimen. So I'm sure this study will be very important, because I think it will be the first one that may provide answers to this potential strategy.

The risk/benefit ratio, I am concerned because of one issue that many people today mentioned, that this is a very convenient regimen, and it is a convenient regimen, and therefore it's going to be--people will be really tempted to use it or a lot of people will be tempted to use it. Providers who are not very experienced with HIV care will be tempted to use it, and the patients may get into trouble if they don't really know the risks that may be associated with this drug.

So I think for the sponsor, they need to be very careful in how they teach and how they talk to the providers and to the patients. Say yes, it is convenient, but on the other hand there's a very important caveat, which is the potential for a serious side effect. So I think the convenience is very helpful but the convenience can also tempt a lot of people to misuse this drug and for problems

to develop.

I think the key to dealing with the side effects and the hypersensitivity issue, I believe is reaching the patients. I always feel that the patients are the ones who really teach the provider, so we have to somehow be able to reach all of our patients and be able to inform them of this potential side effect, and to think of reaching the providers and to think of the providers as a whole team. Now with this focus on adherence, we're thinking more and more of sort of all the team of providers taking care of the patients, to go beyond the doctor and try to maybe get the nursing staff and other people involved in managing our patients to know about this potential side effect, as well.

I think the problem with the rashes, I think mistakes will be made. It's inevitable that people will think that the rash or the manifestations are not the hypersensitivity reactions. Mistakes will be made. I hope that people will be rather cautious and they will err on the side of caution and discontinue medication if they suspect that this may be a hypersensitivity reaction to abacavir.

As for dissemination of information, I mentioned what I thought about dissemination of information. I think the idea of wallet cards is a very, very useful, especially for patients who need to go to an emergency room in the middle of the night or on a weekend or when they can't reach

their provider.

Number six, question number six, the traditional approval package, again I think it's risky with just the pediatric study. It would be really nice to have studies in patients with advanced disease, an experienced population, because I think we've seen all these reports and posters and presentations on salvage therapy, as I think Dr. Matthews mentioned, and it's very difficult to interpret the results, and it would be very nice if there were some studies that really tried to, in an organized manner, look at people who are experienced and with advanced disease.

Finally, on Phase IV studies of abacavir, I think the convenience of the regimen may provide an opportunity to really look at adherence in some Phase IV studies, as well as quality of life issues as well.

Finally, I think coming back to where we started today, about 16-week data versus 24-week data versus 48-week data, I guess I, in thinking about the data presented today, I think for the population that's treatment-naive, what I'm really looking for in a study is the durability of the effects, of the antiviral effects, and 16 weeks does not make sense to me for a naive population. I think at a minimum a 24-week population would make sense to me, because it is a naive patient population.

And I would feel much more comfortable for naive

studies to be looking at 24-week data, because I'm really more interested in durability. I think for advanced--in patients who are experienced, who have multiresistant virus, then I think the earlier data may be quite useful. As we noted, the effect is more likely to be limited and not likely to be as durable. And I'll stop here.

DR. MASUR: Okay. Thank you, Wafaa.

Let's--why don't we just go in order. We can start over here, Ram, and go around, since I think the urgent travel issues are taken care of.

DR. YOGEV: Just for the record, next time I'm leaving at 2:30.

I think identified lists of new population that this triple combination, because of b.i.d. two tablets, are very limited, will be very effective, if as long as we agree that we can have an induction like or a shorter period of time using it, because we know after 16 or 24 weeks it might lose its effect, and then move to a better therapy. Where for example a pediatric patient, when we have a problem with compliance, IV drug user, adolescents, and other groups who have a decreased compliance and an increase in dropout, that might be a very important mechanism to start therapy, to get the effect of that specific one, with the understanding and hopefully part of the education to the physician that this one is really temporary and you have to change in its

approach.

I have a problem, that I sat here for six, seven hours now, and I still don't think that hypersensitivity is well defined, and I hope you approve the drug only in the spring because we don't what to do with influenza in the winter, and it's going to be a major problem, because over-education is a disadvantage.

Every time a person would come to me now with a runny nose and a fever and maybe a rash, and pediatric have six of them per year, we are going to stop this drug. So we are going to stop many more times than we are going to start, and then we have to form yes or no to restart. So I think a major effort has to be put by the company to define this hypersensitivity better, so we know how to deal with it, because otherwise that will pose the risk versus benefit.

To me the population, that there is enough that-- for accelerated approval, is the naive population. The problem is the pediatric, as I mentioned, is working on, as far as I am concerned, too many patients monotherapy. I was especially impressed when you had more than 10,000, if you took away those who were not treated with AZT or treated-- CD4, you didn't find any difference between the two groups, whether it be triple or dual, and you do see that so much in between 152 and 300, led us to believe that dual therapy is

good when we look at 16, even 24.

So I am not sure 24 is the right one for accelerated, but you need to give some points for 16, give you at least some indication. If it's an excellent drug, I think 16 might be good, and then we can change according to what 16 is showing us is different. But to me the studies in pediatrics are interesting at best, but I think the design was not the one I would like to see.

I would like to see a design which will take salvage as a protocol with other drugs, another triple, working on the same mechanism, and on the naive maybe use this one and showing it compared to another triple, to see if really abacavir with its risk of hypersensitivity is better than the ZVD/IDV and 3TC, for example. So another triple nucleoside, if you want even to go in that direction.

And I would like also, there is a claim all the time and we didn't touch on it, or touch on it and run away, on this dementia CSF penetration. I think is very dangerous to take three patient and to suggest there is 30, 40 percent penetration. I don't know what the range is. I think it's not enough, and any study which we are going to design, especially in the salvage patient, should include in it CSF, at least levels.

And some effort should be made if somebody goes into the unfortunate brain of those patient, for pediatric,

whatever, to design a study which will give them for about few, four or five drugs, to just support a study state and then take some even brain tissue to see if it's really working in the right place we want, and I'm not sure CSF does represent it. So those will be my contribution to the Phase IV, if you want to call it like that.

DR. MASUR: Pam?

DR. DIAZ: Most of what I would say has already been said. I'll just make a couple of comments. In particular the magnitude of the risk/benefit ratio is really highly dependent on the group in which one is measuring it, and there are some specific groups, many of which have been mentioned here today, where I believe that risk/benefit ration is high enough to merit the use.

But I would strongly encourage the FDA to work hard with the sponsor to guide physicians and others in which groups they feel this decision merits the use of the drug in particular, and likewise along the lines of the side effect with the hypersensitivity, in particular to work--for the sponsor to work very diligently in developing a program to really further delineate the risk factors associated with this adverse event.

And also to provide physicians, once this is out on the open market, a plan not only that includes recording of any hypersensitivity adverse events, but in particular on

what is necessary and what should be done in terms of data collections, specimen collections, God forbid, autopsy if a death occurs, in being able to help further describe and delineate this, this event, these events, when it occurs.

On the flip side of that, the patients with just--who will present with just rash and perhaps no other adjunct symptoms or signs perhaps associated with this syndrome, I think to guide physicians in what to do in those scenarios and how to monitor patients carefully, time line, et cetera for patients with rash, and with the concern that that may be a heralding event for progression, is also extremely important.

I think some of the other topics have been addressed adequately, as far as I am concerned.

DR. MASUR: Okay. Thank you. Let's go around to Joe.

DR. HOGAN: My concerns are just mostly in some of the--how the analyses relate to how the drug would be used after the accelerated approval. The one issue that I brought up during the question and answer with the sponsor was about the analysis of the pediatric data, and I think this is not entirely clear. I think it's debatable about whether the drug is efficacious in the pediatric population at large, or just in a specific portion of the pediatric population.

And unfortunately I don't think the trial really addresses either of those questions. Number one, it doesn't address whether it's efficacious in the general pediatric population because the combined analysis is not significant at the 5 percent level, even though the effect is dramatic. When the adjusted analysis is presented, my feeling is that the adjustment is improper in the sense that the treatment effect is dramatic for those who start out with viral load over 10,000 but not--there is no real treatment effect for those who start out under 10,000. And in fact, it's just a maintenance effect.

So I think that's a crucial issue, and I know a lot of folks around the table got excited about the pediatric study, and the FDA I think was properly cautious about the result.

I think that the company in the traditional approval needs to investigate this a little bit more carefully. In particular, using the new drug on pediatric patients where the viral load is already less than 10,000 seems to unnecessarily expose them to risk of side effects.

So that's a big concern, and I think that the analysis that adjusts. that shows an overall p-value that's highly significant, should simply be disregarded because it is improperly applied. So on the flip side, if you think there is some efficacy, it's just that it's in a population

with viral load that starts out higher than 10,000.

The problem is, when you do the subgroup analysis, you're stuck with the quandary it's no longer a randomized comparison. So there seems to be some hope there, but I think the analysis needs to be done a little more carefully and maybe even a new cohort started in the group, with a new group over 10,000.

It's also troubling in the pediatric analysis that the dropout rate, which wasn't really adjusted that carefully, is twice as high on the new drug than on the placebo. It's 11 percent versus 5 percent, from what I recall, and I think that this points to a larger issue that has been addressed by several of the panelists about dropout in general.

In a lot of these long-term trials, dropout is a problem. I think due to the hypersensitivity and the possible ramifications of hypersensitivity, some sort of protocol for following dropouts, people who drop out, is warranted. Twenty-one percent dropout or 25 percent dropout on the equivalency trial is extremely troubling, especially since we don't know what the long-term ramifications of re-challenge are; that is that if a person drops out of the study drug and then goes off, maybe gets a study drug some other way later on down the line, is that person also exposed to a re-challenge effect?

So I was a little disappointed in the answer that there is no well-defined protocol for re-following dropouts. I think that needs to be explicitly developed for traditional approval. I think that it may be possible to find these 24 percent of people, and there needs to be some sort of community outreach, re-phone calling, visiting people at their home, something like that, to find these people, because the issue of the hypersensitivity is serious enough to warrant that.

DR. MASUR: I'm sorry. Go ahead.

DR. HOGAN: I just had a couple more comments, but that's okay. I know it's late, but--

DR. MASUR: No, actually now we have an unlimited amount of time.

DR. HOGAN: I see. Well, I won't exercise that limit.

More on the safety issue and sort of tied in with the dropout is, I'll admit that clinicians really are the experts here, but my--I was just a little bit concerned that the--that the labeling or the warning associated with the possible side effects was not quite dramatic enough, especially since this is going to be recommended for general distribution, not within the well-controlled setting of a clinical trial.

You know, it's one of those things that's a lot

easier to criticize rather than create. I really don't know what the method of a more dramatic labeling procedure would be, but I would certainly like to see one. I wasn't totally convinced that a little wallet card would be enough, and something a little more creative, a little more dramatic, given the possible side effects, I think is also warranted.

So just some last notes on possible analyses. I think in the traditional approval it's unfortunate that the 3003 trial, I think the long-term efficacy is really--this sounds a little bit harsh, but I think it's really not going to provide any information about long-term efficacy, and that's too bad. But the switching option really I think will prevent us from seeing anything meaningful long-term on adults in that population.

I think that the investigators, not only do they need to have a protocol for following people who drop out but they also need to know what are the characteristics of people who drop out. That is, if you think about the placebo arm, if a patient enters a trial and they know they've been randomized to either placebo or active drug, and they don't notice that their viral load is dropping, they might be more likely to leave the study.

And I was thinking during the analysis that that might explain actually the differential in the CD4 effect in the 3003 trial. If you have that the people who leave on

the placebo arm are the ones that are doing worse, then you somehow have a more--a better selected, in terms of CD4 count, a better selected population on the placebo arm because you've weeded out those who have low viral loads, if there's any association between viral load and CD4.

And then finally with the analyses methods, I think, you know, I read this with sort of a skeptical eye in the sense that there were some places where I thought the analyses were fishing. I think that the sponsors need to define their analyses a little bit more clearly and use more modern statistical methods.

The imputation methods that they used, filling in the data with last value carried forward, are rather arbitrary and there's a little more modern ways of dealing with that, to be specific for the record, such as maximum likelihood and generalized SMA equations, and Dr. Woolson has developed several of these methods himself. Really they can be implemented on any standard software package, and there's no reason why the data can't be looked at that way, and that will help us maybe understand a little bit better what's happening with the dropouts.

So those are my comments, and also, thanks also to the sponsor and to the FDA for the opportunity to be here. I appreciate it.

DR. MASUR: Okay. Well, those are some useful

statistical considerations.

Joe?

DR. BERTINO: Well, my plane is not until 9:00, and Jeff lives in Washington, so having the last two of us go--I'm not going to comment on number two because I think smarter people than me have already done that.

I think in terms of the risk/benefit for abacavir, I'm very concerned about the hypersensitivity reaction. I think if this drug was in a different class, such as an antibiotic, it wouldn't be approved. I think that my concern is, is what happens in the office setting when it's one-on-one with the pharmaceutical representative and the doctor, and I think people who are going to prescribe this or follow patients who are on this agent really need to be very hypersensitized, too, to this possible side effect.

I think in terms of number four, I think an algorithm would be good, to provide to prescribers a very detailed algorithm. If patients are on A, B and C, and C happens to be abacavir and the patients develop a rash, you do this; if they develop a rash and fever, you do this; if they develop, you know, whatever constellation of symptoms, here's what you would do.

Number five, I liked Dr. Pomerantz's comment about disseminating the education to a lot of people, including pharmacists, and I think patients tend to see their

pharmacists more because sometimes of restrictions, of only being able to get a couple of months' worth of medications at a time. So I think that that would be important information, so the pharmacist can then either call the patient's physician or have the patient go to their physician right away, whatever.

Number six, I don't think the traditional approval package is ready for consideration. I think we need to get full analysis on the 3005 study.

And finally for number seven, just two comments on Phase IV studies. One is, is that in terms of the hypersensitivity mechanism, I think if you look at the data with cefaclor, if you look at the data with phenytoin, the mechanisms of these have been worked out now. I would urge the sponsor to look at the mechanism and the epidemiology of this hypersensitivity reaction, and maybe it could be easily pinned down and you could decide who not to use this drug in. That would be a huge, huge benefit.

One of the--the big concern I have is, and I go back to this again, I know FDA has heard this from me for four years now, is the data in men versus women. A number of years ago in the Federal Register there were some proposed guidelines on studies of drugs in men versus women, including menstrual cycle effects, pre- and post-menopausal studies. These, this publication generated a lot of comment

from big pharma.

And I think I would just say to the sponsor, as I have said to other sponsors, it would be great if someone would take the high road and do these studies in men versus women. For this particular drug, a 54 percent increased exposure of women based on AUC is very concerning to me. I think I would say to the FDA that the reason that these studies aren't done is because the FDA doesn't make the sponsors do the studies.

Women are a huge majority of the population in general in the United States, and certainly lots of women have HIV disease, and I feel very strongly that sex differences studies in terms of kinetics, dynamics, efficacy and toxicity really need to be done for not just this group of agents but in general for drugs. So that's my comments.

DR. MASUR: Good.

MR. BLOOM: I should be clear that the reason I said no is not because I don't believe that this drug may be a valuable drug. I do think it may be valuable, but I really think the sponsor shortchanges themselves and shortchanges the patients when they really don't study it in a way that it's likely going to be used once it's approved.

Because not everyone that's going to be taking this drug is going to be using it, obviously, with AZT/3TC, particularly if they are previously experienced with

AZT/3TC. And I think that's an important point, as we did learn today there are certain populations that this would be inappropriate to use for. But also it would be good to know if it was inappropriate to use for other previously nucleoside experienced people.

But I think the thing that troubles me the most is that I hope Glaxo and the other sponsors that are here and the FDA understand that right now, when a patient decides to start making the commitment to treatment, it's a lifetime commitment. You don't have a choice of making a halfhearted commitment or a partial commitment, but you make a commitment for a lifetime of therapy at the moment.

And with this information given in this application here, you can't possibly know whether this would be your best choice if you are going to initiate therapy. I think we owe it to the people that are treatment-naive, as well as the unfortunately 40,000 new people that are still getting infected every year, that are going to be coming into the market looking for therapy, looking for treatment, to be able to give them the best possible opportunity to effectively treat their disease.

And we have learned, if nothing else, that the first choice has serious consequences for your subsequent choices, and with this kind of information it's very, very difficult to say where this would fit in that dynamic of

choices, and I think that's unfortunate. I think it's unfortunate because I think it shortchanges a drug that potentially could be enormously beneficial, and I think it shortchanges the patients to make educated choices.

I think the timing of this is a little difficult for the hypersensitivity thing because it's flu season, and in the real world there's probably doctors that are going to have a very hard time differentiating between the flu and the hypersensitivity reaction, as well as the rash reaction, which NNRTI's have frequent rash reactions.

This probably is not an appropriate drug to start if you're going to start therapy with one of the NNRTI's that also create rash at the same time, unless there is clearly a way of delineating what is causing the rash and which one is not, particularly since one of the rashes is life-threatening and the hypersensitivityness is life-threatening, so that would be two life-threatening situations to start out with. That would be pretty risky.

And as far as disseminating information, I think that's--you know, that's the key. One of the good things about HIV and AIDS now, and this will be one of Henry's challenges, is that there is the DHHS HIV/AIDS treatment guidelines that make recommendations in terms of treatment. And I hope that the fact that those guidelines exist will give this sponsor and other sponsors incentives to do the

studies so that they can be recommended in the guidelines as an appropriate treatment, and where it will fit in the dynamics.

But it does give you an incentive to have it rated as best treatment, better treatment, less effective treatment. So hopefully everyone is familiar with those treatment guidelines, and if companies aren't going to take it upon themselves to do these kind of studies, hopefully NIH will. But certainly the treatment guidelines have been a godsend in helping people understand this.

And there's a lot of doctors--we all talk about experienced patients--there's still a whole lot of people that aren't experienced in treatment, haven't had treatment at all. That's the majority of the population. So it's really incumbent upon everyone to keep that in mind, and we owe it to them to let them be able to make the best choice possible so that they can live good, full lives and this can be a manageable disease.

I've been living with AIDS for 12 years now. I'm lucky, I've made very good choices. I don't have a lot of resistant virus. I'm not the usual case. So I haven't burned all my options. Other people shouldn't have to burn all their options with bad choices, and make good choices up front, and that's why I'm very disappointed in how this is. I am glad to see that they did a pediatric. I will say that

there was another drug recently approved that also had a pediatric indication, so it's nice to see that we're making progress in that regard. That is something that has been done and they should be commended on that.

As far as the Phase IV studies, you know, it's learning how to use this drug as best as possible, with given the other drugs. You know, those kind of studies unfortunately aren't going to be just carried out by the companies, but they will be carried out by the ACTG and NIH and subsequent studies as that.

And I thank the FDA, and I thank you for letting me be here today.

DR. MASUR: Thanks, Jeff. Fortunately, as far as the antiretroviral guidelines are concerned, Orrin Cone, who has been in the back, hopefully he will take up that challenge, because I think it is important that the information be available so that specific guidelines can be given.

Let me make a few final comments. First of all, as a longstanding committee member, I'm glad to see that the criteria for accelerated and traditional approval are changing as the situation changes, and I hope that we will begin to see more 24-week data rather than just 16-week data for accelerated approval consideration. It sounds like that's the direction we're going, and I would certainly be

enthusiastic about that.

There's clearly a lot of concern with this drug about the dichotomy between immunologic response and virologic response. I was somewhat disappointed not to see more data on--that might be able to separate out which patients had a virologic response without an immunologic response. I hope we will learn more about that, because clearly there are some very important issues coming down the road with other drugs where there is that dichotomy, and with the immunomodulators, where other groups will have to make that decision.

In terms of long-term efficacy, again, I share skepticism that we're going to have more than one study of the studies presented to us that will give us useful data at 48 weeks, and would hope that the agency is going to be very definitive with the sponsor about what needs to be done and how soon it needs to be done in terms of getting another study started.

In terms of the dementia study, I was somewhat disappointed that only three patients, and it wasn't clear to me whether they were patients on the dementia study, had drug levels in the CSF. To some extent, as data becomes available, if there is a correlation between HIV viral load and CSF and dementia, it would be useful to know whether the patients--whether any patients who might have had a response

or appeared to have a response also had a drop in CSF viral load, and happened to be ones who had higher CSF levels. But it's very difficult to know whether there's anything to look forward to in terms of a role for abacavir with dementia or not.

In terms of strategy studies, it's heartening to see that companies are beginning to work together to look at sequential studies with different drugs, and hopefully we will continue to see that.

In terms of safety, I was disappointed at the safety database. While it's been said by a number of people on the panel that it would be great to have some algorithms that indicated what to do, it's not clear to me that the data is there about what to do. We certainly don't have enough data about the eight patients who died. There were distressing holes in knowledge about what was known and what was not known.

It's also not clear to me whether--what the database is that says that continuing a patient on a drug once they have a rash makes the syndrome worse. One of the big issues is going to be, is if a patient has a fever and a rash, on the one hand we're told not to stop and restart, that's when you get into trouble. It's not clear to me how often you get into trouble from just continuing the drug. So the question is, if you're going to try to tough it out,

how long should you tough it out and when should you stop?

And I hope that that data will become available, and that there will, as several people suggested, be some focus studies on those who clearly have the syndrome because they've been re-challenged and gotten into more trouble, and that there will be some comparative studies looking at patients who have fever or rash due to other drugs compared to this hypersensitivity reaction, to see if we can develop more data that would help identify this syndrome specifically.

The mechanism of the adverse reaction, we didn't hear very much about that, what the sponsor is doing to look into the mechanism, but I would hope that at some of the treatment sites that there will be a plan that if a patient has this syndrome, there will be some specific studies looking at immunology, looking at hemodynamics, depending on the severity, so that we get some more information, because right now when we have simply a random observational data base, we are obviously not going to get very far in terms of understanding what this is, how to treat it if it occurs, or perhaps how to prevent it.

But in any event, I think that there is a lot of useful data here, and we'll look forward to what the sponsor negotiates with the agency and hope that the agency can come up with a very concrete plan that will help us all have the

information that we need.

So unless one of the committee members has another comment, we again appreciate the candor of the sponsor in providing all the data and the pre-meeting material. We appreciate the agency analysis. And on behalf of the committee, we thank everybody for attending, and we'll look forward to seeing you at the next meeting.

[Whereupon, at 4:12 p.m., the meeting was concluded.]

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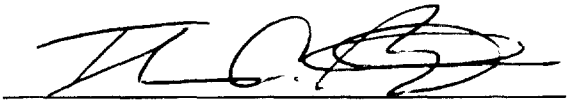
CERTIFICATE

I, **THOMAS C. BITSKO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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